as 1 H singlets at 8.23 and 8.33. Anal. Calcd for $C_{15}H_{17}N_5 \cdot 0.2H_2O$: C, 66.50; H, 6.47; N, 25.85; H_2O, 1.33. Found: C, 66.60; H, 6.30; N, 25.82; H_2O, 1.02.

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Supplementary Material Available: Additions to the Experimental Section (general procedures, method of ^2H NMR measurements, additional details on the structural assignment of 8, preparation of 17, and alkylation of adenines under neutral conditions), a 360-MHz ^1H NMR spectrum of 10 including D_2O exchange, and MNDO calculations on 1 and 4 (7 pages). Ordering information is given on any current masthead page.

Synthetic Studies on the Mevinic Acids Using the Chiron Approach: Total Synthesis of (+)-Dihydromevinolin

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A general strategy for the synthesis of the mevinic acids starting from L-glutamic acid as a chiral template is presented. The octahydronaphthalene ring system of dihydromevinolin and mevinolin is constructed from an intramolecular Diels–Alder cycloaddition involving a butenolide. The lactone portion is elaborated from a cyclopentanone by a Baeyer–Villiger oxidation with bis(trimethylsilyl) peroxide.

In 1975, after testing some 8000 strains of microorganisms for inhibition of in vitro sterol synthesis, Endo and co-workers[1] at the Sankyo laboratories isolated three active compounds from the culture broth of the fungus *Penicillium citrinum*. The main compound, ML-236B, was also isolated as an antifungal agent from *P. brevicompactum* by Brown and co-workers[2] at Beecham Pharmaceuticals and was named compactin (1). A second, more active compound, mevinolin, was later isolated from *Monascus ruber* by Endo[3] and from *Aspergillius terreus* by Alberts and co-workers[4] at Merck, Sharpe & Dohme. Two related compounds, dihydrocompactin (3)[5] and dihydromevinolin (4),[6] were subsequently isolated as minor metabolites from the cultures of these fungi. These four fungal metabolites are part of a family of compounds called the mevinic acids[7] (Figure 1).

Since their discovery, compactin (1) and mevinolin (2) have attracted considerable attention due to their biological activity as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterogenesis in man. Mevinolin, presently marketed under the trade name Mevacor, is one of the most clinically useful hypocholesterolemic agents, and it is manufactured by a fermentation process. Dihydromevinolin (4), which exhibits biological activity similar to mevinolin, is produced in small quantities during the fermentation; hence it has not been developed as a clinical candidate.

The unique structural features of the mevinic acids combined with their important biological action has fostered a large number of studies aimed at their total synthesis as well as the production of structural analogues.[7] To the best of our knowledge there are at present two total syntheses of dihydromevinolin,[8,9] a formal synthesis[10] and a semisynthesis from mevinolin via selective reduction of one of the double bonds.[11] In view of the latter report, the existing syntheses of mevinolin[12] can also be considered as viable approaches to dihydromevinolin.

Examination of the structures of the mevinic acids reveals unique stereochemical and functional features that present certain challenges in stereocontrolled synthesis.[13] The possibility of obtaining enantiomerically pure compounds adds another dimension of complexity to the synthesis plan.

The first total synthesis of dihydromevinolin was accomplished by Falck and Yang in 1984.[8] In this synthesis, a racemic octahydronaphthalene intermediate was con-

(1) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *26*, 1346.
(2) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans.* **1976**, 1165.
(3) Endo, A. *J. Antibiot.* **1979**, *32*, 854.
(4) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C. H.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A. A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schönberg, G.; Hensens, O.; Hirschfield, J.; Hoogsteen, K.; Liesch, J. *Proc. Nat. Acad. Sci. U.S.A.* **1980**, *77*, 3957.
(5) Lam, Y. K. *J. Antibiot.* **1980**, *33*, 334.
(6) Albers-Schönberg, G.; Joshua, M.; Lopez, M. B.; Hensens, O. D.; Springer, J. P.; Chen, J.; Ostrove, S.; Hoffman, C. H.; Alberts, A. W.; Patchett, A. A. *J. Antibiot.* **1981**, *34*, 507.
(7) For a recent review, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4209.
(8) Falck, J. R.; Yang, Y. L. *Tetrahedron Lett.* **1984**, *25*, 3563.
(9) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586.
(10) Davidson, A. H.; Jones, A. J.; Floyd, C. D.; Lewis, C.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1987**, 1786. Davidson, A. H.; Floyd, C. D.; Jones, A. J.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1985**, 1662.
(11) DeCamp, A. E.; Verhoeven, T. R.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3207.
(12) (a) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596. (b) Clive, D, L. J.; Keshava Murthy, K. S.; Wee, A. G. H.; Siva Prasad, J.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914. (c) Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811.
(13) For an excellent monograph, see: Corey, E. J.; Cheng, X.-M. *The Logic of Organic Synthesis*; Wiley: New York, 1989.

0022-3263/90/1955-5766$02.50/0

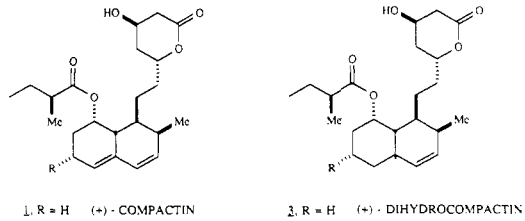


Figure 1. Structures of mevinic acids.

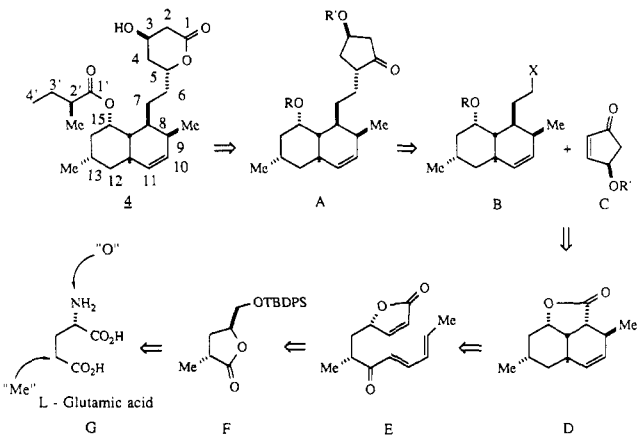


Figure 2. Disconnective analysis of dihydromevinolin and the emergence of chirons.

densed with a primary iodide derived from a carbohydrate, via phenyl sulfone anion technology. Further elaboration of the mixture of diastereomers produced the desired isomer corresponding to dihydromevinolin, the other isomer having an enantiomeric octahydronaphthalene portion being discarded. A similar strategy had been used by Falck and co-workers[14] for the synthesis of dihydrocompactin. Hecker and Heathcock[9] reported a total synthesis of dihydromevinolin in which a racemic octahydronaphthalene unit was generated as a fully functionalized intermediate. The desired enantiomer was obtained after separation of the *O*-methyl mandelate esters, and it was further transformed into a mixture of open-chain epimeric δ-hydroxy esters corresponding to the δ-lactone portion. Cyclization of the correct isomer then produced the intended target **4**.

The synthesis of the enantiomerically pure octahydronaphthalene unit previously obtained by Hecker and Heathcock[9] was reported by Davidson and co-workers,[10] utilizing an intramolecular Diels–Alder reaction approach that was independently conceived and strategically similar to ours discussed in this paper.

Our synthesis strategy was aimed at devising a general and stereocontrolled approach to all four mevinic acids through the creation of an appropriately functionalized octahydronaphthalene intermediate. An added design feature was the intentional adoption of the chiron approach,[15,16] where advanced intermediates could be related to, and constructed from, chiral synthons that are in turn readily available from optically active starting materials. Strategic bond cleavage in dihydromevinolin leads to the octahydronaphthalene unit B and the (*R*)-4-hydroxycyclopentenone C to be joined as nucleophilic and electrophilic components, respectively, in the proposed synthesis (Figure 2). Subunit B, with its full complement of stereogenic centers, was envisaged to arise from the tricyclic lactone D by an intramolecular Diels–Alder reaction[17] of the butenolide diene E followed by stereochemical adjustment and chain extension. Subunit E was to be built up from the chiron F, easily obtainable from L-glutamic acid.[18] Several aspects of this plan are of interest and warrant some commentary. Firstly, it is clear that the key step in the construction of the pivotal tricyclic lactone D was predicated upon the successful intramolecular Diels–Alder reaction that was expected to proceed via an exo transition state[19] as shown in Figure 3. The other geometrically less favored pair are is shown. This would produce the intended lactone D with the correct sense of chirality at all but one site, which fortunately is situated so as to permit an epimerization to the more stable C-8 epimer following opening of the lactone. The Davidson route[10] also proceeds via an intramolecular Diels–Alder strategy, whereby a tricyclic lactone is produced in which the carbonyl group corresponds to the C-13 methyl group. With regard to the synthesis of E, it is of interest to comment on the ability to "see" the L-glutamic acid framework in which the amino group must be replaced by oxygen and the C-4 carbon must be methylated with high stereoselectivity. This can be easily accomplished through the intermediacy of (4*S*)-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-4-butanolide, which is readily available from L-glutamic acid.[18]

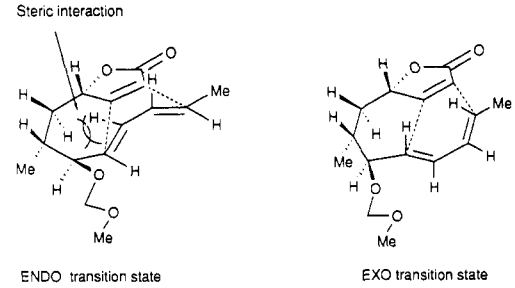


Figure 3. Pictorial representation of endo and exo transition states in the intramolecular Diels–Alder reaction of **14**.

With regard to the assembly of the mevinic acid structures, one of the two previous syntheses of dihydromevinolin[8] and the majority of other syntheses of analogues[7] have adopted a strategy whereby an electrophilic six-carbon lactone equivalent was joined with a nucleophilic octahydronaphthalene unit having an appropriate one-carbon functionality. In the other synthesis[9] an octahydronaphthalene aldehyde was coupled with a β-ketophosphonate corresponding to the lactone portion. The literature is abound with reports of the synthesis of the lactone portion from a variety of optically active precursors.[20]

(14) Yang, Y. L.; Manna, S.; Falck, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 3811.

(15) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1983.

(16) Hanessian, S. *Aldrichimica Acta* **1989**, *22*, 3.

(17) For reviews on the Diels–Alder reaction including intramolecular variants, see: Ciganek, E. *Org. React.* **1984**, *32*, 41. Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181.

(18) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5072. Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5627.

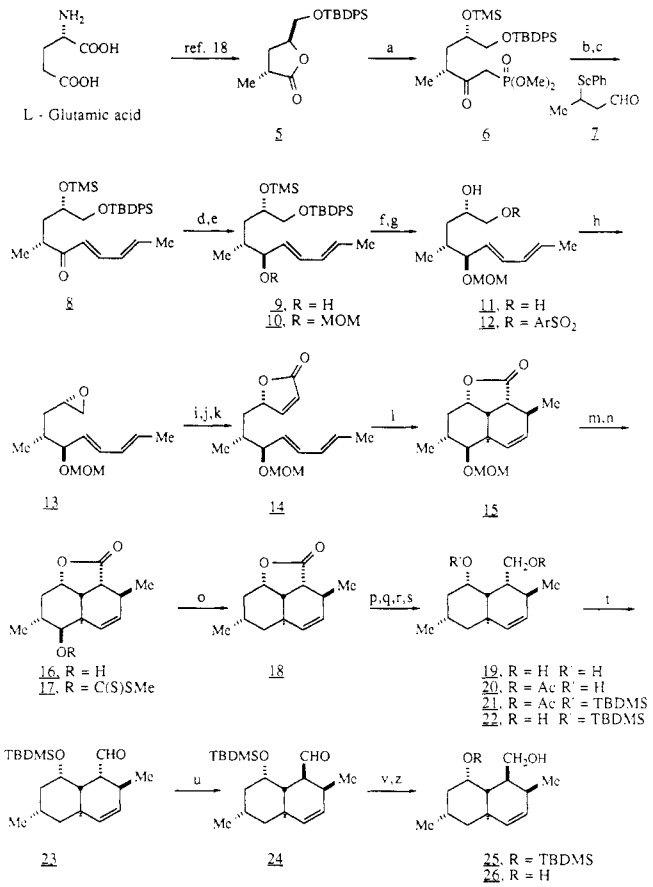
(19) For a related reaction and discussions on the mechanism of the intramolecular Diels–Alder reaction, see: (a) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670. (b) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. Taber, D. F. *Intramolecular Diels-Alder and Alder-Ene Reactions*; Springer-Verlag: Berlin, 1984; pp 1–60.

We resoned that the lactone portion of dihydromevinolin could be generated late in the sequence by a site-selective Baeyer–Villiger oxidation of a corresponding disubstituted cyclopentanone, as can be found in A (Figure 2). In order to implement this novel route to the mevinic acids, we required access to C in optically pure or enriched form, as well as a suitable coupling strategy based on a Michael addition. With the above-mentioned ideas in mind, and being cognizant of the potential pitfalls the overall strategy might have in store for us, we set out to test the plan.

As mentioned previously, optically pure lactone **5** is available in crystalline form.[18] In order to generate the Diels–Alder reaction precursor E (Figure 2), we had to introduce a diene and a dienophilic butenolide motif. Treatment of **5** with dimethyl lithium methylphosphonate, followed by addition of trimethylsilyl chloride, afforded the open-chain β-ketophosphonate derivative **6** in high yield (Scheme I), presumably due to a faster rate of silylation of the hydroxyl group compared to lactol formation. Since formation of the diene with crotonaldehyde proved to be inefficient, mainly due to low yields, an indirect but highly efficient approach was developed by using 3-(phenylseleno)butanal (**7**) as a crotonaldehyde equivalent.[21] Sequential Horner–Emmons reaction and oxidative elimination of the product led to the desired diene **8** as the trans–trans isomer in high overall yield. The ketone function, having served its intended role in the formation of the diene, had to be modified or removed before the butenolide segment was elaborated. A number of reducing agents were tried including sodium borohydride, but a mixture of epimeric alcohols was produced. Since the configuration at this center was considered to be important for the stereochemical outcome of the Diels–Alder reaction, it was imperative that we proceed with a pure isomer, even if it was isomeric to the one that would lead to the desired tricyclic compound of general structure D. We could at least have the option of a configurational inversion at the level of the diene and a second chance at the intramolecular Diels–Alder reaction.

Reduction of **8** with L-selectride produced a single isomer, which was later shown to have the *S* configuration as in **9** (vide infra). At this point, a decision had to be made concerning the choice of protective group, bearing in mind that in addition to withstanding the conditions of the Diels–Alder reaction, it could also play a role in its stereochemical outcome. After experimenting with a number of protective groups (benzyl, benzyloxymethyl), we chose to proceed with the methoxymethyl (MOM) group. The MOM ether **10** was transformed into the epoxide **13** using standard reactions,[18] and the latter was converted into the butenolide **14** by a protocol previously developed in our group.[18,22] Refluxing a xylene solution

Scheme I[a]



[a] (a) $(MeO)_2P(O)CH_2Li$, THF, −78 °C to −20 °C, then Me_3SiCl, overnight, 83%; (b) NaH, **7**, THF, 0 °C, 1 h; (c) H_2O_2, CH_2Cl_2, 20 min, then aqueous $NaHCO_3$, room temperature, 82% (two steps); (d) L-Selectride, THF, −78 °C, 25 min, 62%; (e) $EtN(i\text{-}Pr)_2$, MOMCl, CH_2Cl_2, 0 °C to room temperature, 3 h, 85%; (f) TBAF, THF, 0 °C to room temperature, 2 h, 98%; (g) $ArSO_2Cl$, Py, CH_2Cl_2, −5 °C, 64 h, 75%; (h) MeONa, MeOH, CH_2Cl_2, 0 °C, 40 min, 87%; (i) LDA, $PhSeCH_2COOH$, −15 °C to room temperature, 23 h; (j) 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide, CH_2Cl_2, 0 °C to room temperature, 3 h; (k) H_2O_2, CH_2Cl_2, then aqueous $NaHCO_3$, 0 °C, 30 min, 70% (three steps); (l) *o*-xylene, reflux, 6 days, 65%; (m) HCl, 6 M THF, 40 °C, 19 h, 95%; (n) NaH, CS_2, THF, 0 °C, then CH_3I, 4 h; (o) *n*-Bu_3SnH, AIBN, toluene, reflux, 35 min, 68% (two steps); (p) LAH, THF, 0 °C, 30 min, 94%; (q) Ac_2O, Py, 0 °C to room temperature, 20 h, 91%; (r) TBDMSOTf, Et_3N, CH_2Cl_2, room temperature, 30 min, 85%; (s) LAH, THF, 0 °C, 40 min, 90%; (t), $(COCl)_2$, DMSO, CH_2Cl_2, −55 °C to −10 °C, then **22**, 20 min, Et_3N, −10 °C, 5 min, 84%; (u) K_2CO_3, MeOH, sealed tube, 100 °C, 19 h, 53% (40% recovered **23**); (v) $NaBH_4$, MeOH, room temperature, 5 min; (z) CH_3CN/aqueous HF (95:5), room temperature, 4 h, 91% (two steps).

containing **14** for 6 days led to the tricyclic lactone **15** in 65% yield. Although detailed spectroscopic data on this product were reassuring, we did not as yet know which of the two epimeric C-5 alcohols we had obtained during the reduction. That this was indeed crucial was evident from the following planned diversion from the synthesis.

Since the reduction of **8** with sodium borohydride had produced two epimeric alcohols that could be separated, we carried the other alcohol through to the Diels–Alder reaction stage. We were intrigued that the MOM ether corresponding to the epimeric **14** produced a mixture of tricyclic lactones, in which the desired isomer **15** (except for the inverted configuration at C-12 (dihydromevinolin

(20) See, for example: (a) David, D.; Gesson, J. P.; Jacquesy, J. C. *Tetrahedron Lett.* **1989**, *30*, 6015. Prugh, J. D.; Rooney, C. S.; Dean, A. A.; Ranjit, H. G. *J. Org. Chem.* **1986**, *51*, 648. Ho, P. T.; Chung, S. *Carbohydr. Res.* **1984**, *225*, 318. Yang, Y. L.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305. Lee, T. J. *Tetrahedron Lett.* **1985**, *29*, 1255. Roark, W. M.; Roth, B. D. *Tetrahedron Lett.* **1988**, *29*, 1255. (b) Guindon, Y.; Yoakim, C.; Bernstein, M. A. *Tetrahedron Lett.* **1985**, *29*, 1185. Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3994. Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101. (c) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Fehlhaber, H. W.; Jendralla, H., Kessler, K.; Saric, R.; Schüssler, H.; Teetz, V.; Weber, M.; Wess, G. *Tetrahedron Lett.* **1988**, *29*, 2563. Bennett, F.; Knight, D. W. *Tetrahedron Lett.* **1988**, *29*, 4625. Roth, B. D.; Roark, W. H. *Tetrahedron Lett.* **1988**, *29*, 1255. Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 736. Prasad, K.; Repic, O. *Tetrahedron Lett.* **1984**, *25*, 3391. Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1983**, *47*, 1982.

(21) Hanessian, S.; Hodges, P. J.; Sahoo, S. P.; Roy, P. J. *Tetrahedron Lett.* **1986**, *27*, 2949.

(22) Hanessian, S.; Hodges, P. J.; Murray, P. J.; Sahoo, S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 754.

numbering)) was predominant, but by no means practically interesting. Definitive evidence in favor of the structure of the original intramolecular Diels–Alder reaction product obtained from **14** was secured from a single-crystal X-ray analysis of the deprotected derivative **16**.[23] The formation of tricyclic hydrindene lactones and hexahydronaphthalene lactones by intramolecular Diels–Alder cyclocondensations of butenolides with appropriate dienic appendages has been previously reported.[19a,24]

Having shown that the synthesis plan had effectively produced the versatile advanced intermediate **15**, we had the choice of proceeding with the synthesis of dihydromevinolin by a deoxygenation reaction or opting to dehydrate the alcohol, thus opening the way to the mevinolin series. Both of these options were exercised with success. Deoxygenation of **16** was achieved through the free radical removal of the xanthate group in **17**, a process pioneered by Barton and McCombie.[25] It now remained to adjust the stereochemistry at C-1 in **18** or a suitable derivative, en route to the hydroxymethyl derivative **25**, whose physical constants could be correlated with those reported by Hecker and Heathcock.[9] Since epimerization of the lactone **18** would not be a favorable process in spite of the "all-axial" orientation of the functional groups, we chose to adjust the stereochemistry at the oxidation state of an aldehyde. Although the lactone **18** could be cleanly reduced with Dibal, the product was exclusively the cyclic hemiacetal, and all efforts to trap a hydroxyl-substituted aldehydo derivative failed. The problem was solved in an indirect way by a protocol of preferential protection and deprotection, which produced **23**. It is of interest to point out that during an attempt to preferentially protect the primary alcohol as the *tert*-butyldimethylsilyl ether, a nonnegligible proportion of the secondary TBDMS ether was formed by intramolecular migration. Although, in principle, this was an attractive possibility for a subsequent oxidation of the primary alcohol, the necessity to separate the two ethers urged us to change the nature and order of the protective groups. Thus, acetylation of the primary alcohol, silylation, deacetylation, and oxidation produced the desired **23** with no difficulty. No acetyl migration was observed under the conditions of acetylation and silylation.

What was regarded as a trivial epimerization of an "axial" aldehyde in **23** to the equatorial isomer in **24** proved to be not so trivial. After much experimentation it was found that heating **23** in methanolic potassium carbonate in a sealed tube for 19 h at 100 °C gave the desired aldehyde **24** in 53% isolated yield, with excellent recovery (40%) of unchanged **23**. The same phenomenon was seen with the corresponding MOM ether, except that the products could not be separated by chromatography as in the case of **23** and **24**. It is of interest that Hecker and Heathcock[9] had succeeded in epimerizing an acetoxymethyl ketone related to **23** (96:4 at equilibrium) in neat DBU at 95 °C for 2 days.

For the purposes of sample comparison, **24** was reduced to **25** and the latter was desilylated to the diol **26**, which was found to have physical constants (NMR, $[\alpha]_D$) in excellent agreement with those reported by the Berkeley[9] and Cardiff[10] groups.

With the octahydronaphthalene portion of dihydromevinolin in hand, we next considered various options for the introduction of the lactone moiety en route to the intended target. Previous syntheses in this area have utilized a number of approaches for the attachment of the lactone portion.[7] Except for the Hirama synthesis of compactin,[26] where the entire backbone was first built and then subjected to intramolecular cycloaddition to produce the bicyclic target with a pendant enthano bridge and a lactone moiety, all other approaches have relied on the synthesis of the bicyclic portion first and the attachment of the lactone portion or its equivalent afterward.[7] In view of the nature of the lactone portion, a number of syntheses have involved starting materials derived from carbohydrates after appropriate deoxygenation.[20a] Shorter chains arising from chiral, nonracemic hydroxy acids[20b] and other sources[20c] have also been used. The lactone portion has also been constructed by using a hetero-Diels–Alder reaction, a protocol extensively investigated by Danishefsky and co-workers[27] and recently applied to the compactin–mevinolin problem.[12a,27]

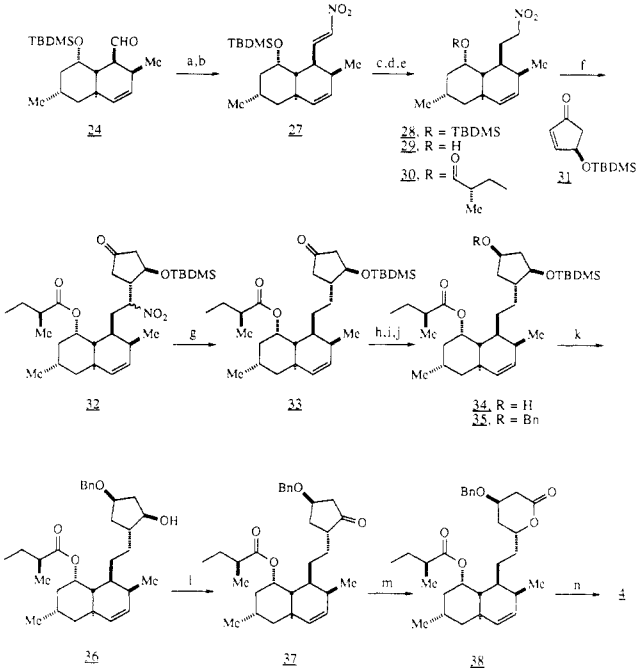
We envisaged the lactone portion of dihydromevinolin to arise from a Baeyer–Villiger oxidation of a disubstituted cyclopentanone appended to the octahydronaphthalene portion by an ethano bridge as shown in Figure 2. To the best of our knowledge, such an approach to the lactone portion of a preassembled dihydromevinolin precursor has not been reported.[28] Such a strategy would involve the stereocontrolled Michael-type conjugate addition of ethano nucleophile B on an optically active 4-substituted cyclopentenone C,[29] followed by functional group adjustments. In spite of its aesthetic appeal, a number of potential problems were evident at the outset, not the least of which was the prospect of effecting a Baeyer–Villiger-type oxidation of the cyclopentanone moiety in A in the presence of a double bond (Figure 2). A second problem to be addressed was the nature of the nucleophilic activating group X in intermediate B, its subsequent removal from the product of Michael addition, and the feasibility of functional group adjustments en route to the desired cyclopentanone. Finally, a crucial decision had to be made with regard to the appropriate place in the sequence in which acylation with a 2(*S*)-methylbutyryl group would be effected.

Extensive model studies[30] were done in this regard using the sulfone[31] and nitro groups[32] as sources of carbanions. For the purposes of our strategy shown in Figure 2, we opted for the nitroalkane route (X = NO_2), as shown in Scheme II. Treatment of **24** with nitromethane anion followed by mesylation of the resulting mixture of nitro alcohols gave the nitroolefin **27**.

It is at this stage in the sequence that we decided to remove the TBDMS group and to introduce the required ester function, cognizant of the sterically demanding environment of the axial secondary alcohol in question.[9,33] Reduction of **27** with sodium borohydride followed by

(23) Bélanger-Gariepy, F.; Roy, P.; Hanessian, S.; Brisse, F. *Acta Crystallogr.* **1989**, *C45*, 145.
(24) Burke, J. D.; Manin, D. R.; Oplinger, J. A.; Baker, J. P.; Abdelmagid, A. *Tetrahedron Lett.* **1984**, *25*, 19.
(25) Barton, D. H. R.; McCombie, S. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574.
(26) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251.
(27) Danishefsky, S. J.; Simoneau, B. *Pure Appl. Chem.* **1988**, *60*, 1555. Danishefsky, S. J.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.
(28) For related oxidations to produce analogues in this series, see: Prasad, K.; Repic, O. *Tetrahedron Lett.* **1984**, *25*, 2435.
(29) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348; *Tetrahedron Lett.* **1983**, *24*, 1187.
(30) Hanessian, S.; Carganico, G.; Petrini, M. Unpublished results.
(31) For reviews on sulfone anion methodology, see, Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. Kocienski, P. *Phosphorus Sulfur* **1983**, *24*, 97 and references cited therein.
(32) See, for example: Barrett, A. G. M.; Graboski, G. P. *Chem. Rev.* **1986**, *86*, 751. Bauer, H. H.; Urbas, L. *The Chemistry of the Nitro and Nitroso Group*; Feuer, H., Ed.; Interscience: New York, 1970; Part 2, p 75 and references cited therein.
(33) Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538.

Scheme II[a]

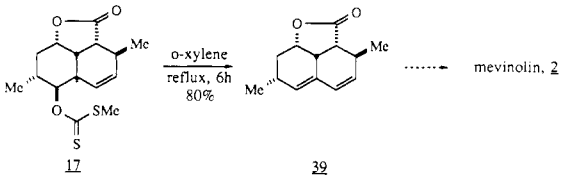


[a] (a) MeONa, $MeNO_2$, MeOH, room temperature, 2 h, 73%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 85%; (c) $NaBH_4$, $CHCl_3$/*i*-PrOH (27:1), room temperature, 40 min, 90%; (d) CH_3CN/aqueous HF (4:1), room temperature, 24 h, 93%; (e) (*S*)-2-methylbutyric anhydride, DMAP, 40 °C, 20 min, 70%; (f) Amberlyst A-21, Et_2O, **31**, room temperature, 2 h, 70%; (g) *n*-Bu_3SnH, AIBN, reflux, 30 min, 55%; (h) $NaBH_4$, THF/*i*-PrOH (4:1), −78 °C to room temperature, overnight, 80% (two epimers); (i) (minor epimer), DEAD, HCOOH, PPh_3, 0 °C then room temperature, 45 min 70%; (j) NaH, TBAI, BnBr, THF, 0 °C to room temperature, 18 h, 80%; (k) CH_3CN/aqueous HF (9:1), room temperature, 90 min, 85%; (l) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, 10 min, then **36**, 15 min, Et_3N, −60 °C, 76%; (m) bis(trimethylsilyl) peroxide, BF_3·Et_2O, CH_2Cl_2, room temperature, 90 min, 78%; (n) BCl_3, CH_2Cl_2, −78 °C, 8 h, 42%.

desilylation in acetonitrile containing aqueous HF led to the expected nitro alcohol derivative **29** in high overall yield. In our hands, acylation was best effected with (*S*)-2-methylbutyric anhydride[33] in the presence of DMAP to give **30**.

The critical Michael addition was done by allowing the nitroalkane **30** to come into contact with (*R*)-4-[(*tert*-butyldimethylsilyl)oxy]cyclopent-2-enone[29] (**31**) (~87% optical purity) in the presence of Amberlyst A-21 in the minimum volume of ether, which is allowed to evaporate. This remarkable reaction, first reported by Rosini and co-workers[34] for the reaction of nitroalkanes with aldehydes and α,β-unsaturated aldehydes, can also be achieved in the presence of neutral alumina.[34,35] The extreme mildness of the conditions of condensation, coupled with the efficiency of the reaction in spite of the functionalized nature of the reacting partners, warrants attention for related applications in the future. The epimeric mixture of nitroalkanes **32**, thus formed in 70% yield was treated with tributyltin hydride in the presence of a catalytic amount of AIBN to give the corresponding des-nitro derivative **33** in 55% yield. The radical-induced removal of a nitro group is of interest, since this reaction is normally facile for α-nitro ketones and tertiary nitroalkanes.[36]

Scheme III



We were now faced with the nontrivial interchange of functional groups in **33**, in order to place the carbonyl function in its expected position. The most practical procedure involved reduction of **33** with sodium borohydride, which was found to give a ~5:1 mixture of alcohols in favor of the desired *R* isomer **34**. The small proportion of the minor *S* isomer was easily separated by column chromatography and "inverted" via a Mitsunobu reaction.[37]

The choice of the new protective group was considered to be critical, since it had to withstand the transformations yet to come and ultimately be cleaved without affecting the lactone and ester groups or suffering irreversible β-elimination, thus seriously jeopardizing the entire operation. We conservatively chose the benzyl ether group, since in their synthesis of compactin, Grieco and co-workers[38] had previously used a methyl ether as protective group at the same position and had succeeded in removing it in a Lewis acid catalyzed reaction albeit in modest yield.

In the event, **34** was transformed into the corresponding benzyl ether, and the TBDMS group cleaved in two high-yielding steps to afford **36**. Swern oxidation[39] then gave the ketone **37**, which was subjected to a normal Baeyer–Villiger oxidation of MCPBA. Not surprisingly, a mixture of products resulting from indiscriminate oxidation of the ketone and olefinic functions was obtained. Having somewhat anticipated this course of events, we had initiated a parallel study[30] of the oxidation of 3-(benzyloxy)-5-(2-ethano-3-cyclohexenyl)cyclopentanone as a model with bis(trimethylsilyl) peroxide[40] in the presence of BF_3·Et_2O. This combination of reagents had been previously used[41] in the oxidation of ketones to lactones in the presence of olefins, albeit with simple systems compared to **37**. Treatment of **37** with this oxidizing mixture led to the expected lactone **38** in 78% isolated yield, thus bringing the synthetic sequence one step closer to its conclusion. The final deprotection step was effected with boron trichloride in dichloromethane[42] at −78 °C to afford a 42% yield of crystalline dihydromevinolin (50% based on recovered starting material). Unfortunately, many trials did not improve this yield, which was also the case in the Grieco synthesis[38] where a methyl ether was the offender.

Protective groups notwithstanding, the strategy shown in Figure 2, which uses L-glutamic acid as a starting material[10,16] (a chiral template), is of general applicability for the synthesis of a variety of mevinic acids. In this regard, we were able to utilize **16** as a common precursor for the synthesis of an advanced intermediate in the mevinolin

(34) Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* **1983**, 1014. Rosini, G.; Marotta, E.; Ballini, R.; Petrini, M. *Synthesis* **1986**, 237. Ballini, R.; Petrini, M. *Synthesis* **1986**, 1024.

(35) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261.

(36) Otani, S.; Hashimoto, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1825. Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705. Ono, N.; Kaji, A. *Synthesis* **1986**, 693. Ono, H.; Fujii, M.; Kaji, A. *Synthesis* **1987**, 532.

(37) Mitsunobu, O. *Synthesis* **1981**, 1.

(38) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403.

(39) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(40) Cookson, P. G.; Davies, A. G.; Fazal, N. *J. Organomet. Chem.* **1975**, *99*, C31.

(41) Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029. Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902.

(42) Bonner, T. G.; Saville, N. M. *J. Chem. Soc.* **1960**, 2851.

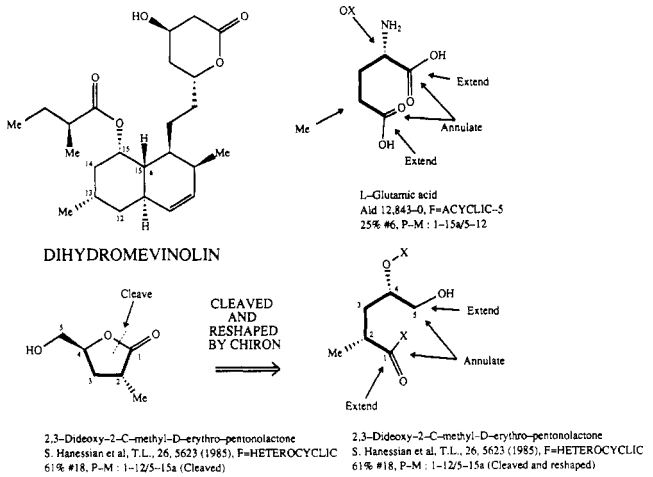


Figure 4. Chiron analysis of dihydromevinolin using the computer-assisted precursor selection option in the CHIRON program (Version 4.2). Matching, cleaving, and reshaping of precursor structures to converge with the C-12 → C-15a substructure in the target.

series as well. Transformation into the xanthate **17** and elimination by refluxing in xylene afforded the hexahydronaphthalene intermediate **39** in 80% yield (Scheme III). In spite of the anti orientation of the xanthate ester and the angular hydrogen atom, the Chugaev reaction proceeded in high yield, as has been observed in other cases.[43] Thus, our initial plan to devise a general approach for the synthesis of all naturally occurring members (and possibly analogues) in the mevinic acid series was realized.[44]

An important aspect in the design of a synthetic scheme for a given target molecule relies on our powers of perception, on the type of reaction in strategic bond forming steps, and in the choice of starting materials.[16] Thus, the choice of L-glutamic acid as a chiral template for the synthesis of the mevinic acids[10] is not entirely obvious, particularly in view of the apparent absence of functional overlap with the octahydronaphthalene portion of dihydromevinolin (Figure 2). It is only at the level of chiron F that a "visual connection" can be made with the above-mentioned substructure, since the C-2 methyl group and the C-4 oxygen atom can be related to their counterparts in ring A of the target. With the discovery of such a chiron, a strategy can be formulated that relies on an intramolecular Diels–Alder reaction of E. In other words, the nature of chiron F dictates the subsequent chemistry, hence the strategy.

Alternatively, it could also be argued that it was the decision to construct the octahydronaphthalene portion of dihydromevinolin using an intramolecular Diels–Alder reaction that led us to intermediates D and E and eventually to chiron F. On may therefore ask: is it the choice of starting material or the desire to carry out a specific type of critical bond-forming step that dictates the strategy (i.e., intramolecular Diels–Alder reaction E → D)?

Figure 4 shows an output of the computer assisted precursor selection (CAPS) option in the CHIRON program (Version 4.2), where chiral nonracemic precursors were searched in a precursor data base available in the program. It is of interest that a chiral butanolide precursor related to **5**, and, more importantly, the original chiral template L-glutamic acid were among many starting materials suggested by the program. This heuristic analysis, based on carbon skeletal, functional, and stereochemical convergence and adjustments between precursor and target substructures, is done in a matter of seconds, far surpassing the visual deductive process. The otherwise difficult problem of "seeing" through molecules can be greatly simplified by using the program, thus aiding in the formulation of a viable synthesis plan.[45]

Experimental Section

^{1}H NMR spectra were recorded on Varian 300 and Bruker 400 MHz instruments, using deuteriochloroform as solvent (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Infrared spectra were recorded with a Perkin-Elmer 781 spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. Combustion analyses were performed by Guelph Laboratories Ltd., Guelph, Ontario, Canada. Chromatography was done by the flash method.[46] X-ray analysis was done on the NONIUS-ENRAF CAD-4 diffractometer using graphite-monochromatized Cu Kᾱ radiation, and the structure was solved by using the MULTAN program. Mass spactra were recorded at low and high resolution on a Kratos MS-50 TATC instrument.

(2*R*,4*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-methyl-4-butanolide (5). To a solution of diisopropylamine (3.95 mL, 28 mmol) in 120 mL of dry THF at 0 °C was added slowly 1.55 M BuLi (18 mL, 28 mmol). After several minutes, the solution was cooled to −78 °C and a solution of (4*S*)-4-*tert*-butyldiphenylsilyloxymethyl-4-butanolide[18] (10 g, 28 mmol) in 40 mL of dry THF was added over a period of 5 min. After 30 min at −78 °C, iodomethane (3 mL, 42 mmol) was added, the cold bath was then removed, and the solution was stirred for a further 20 min. Distilled water (400 mL) was then added, and the solution was extracted with a total of 50 mL of diethyl ether. The ether layer was washed successively with 1 M hydrochloric acid (3 × 50 mL) and saturates sodium chloride solution (50 mL). After being dried over anhydrous sodium sulfate, the solution was evaporated to give a yellow syrup. The procedure was repeated with two 10-g portions of the starting material. The crude product was purified in three portions on the same flash column (1:20 EtOAc–hexanes). The resulting product was recrystallized from 180 mL of distilled hexanes to give 24.1 g (77%) of white crystals: mp 76–77 °C; $[\alpha]^{25}_D$ + 35° (*c*, 2.0, $CHCl_3$); IR (Nujol) 1775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68–7.64 (m, 4 H, Ar), 7.48–7.37 (m, 6 H, Ar), 4.57–4.51 (m, 1 H, H-4), 3.85 (dd, 1 H, *J* = 11.3, 3.5 Hz, H-5), 3.66 (dd, 1 H, *J* = 11.3, 3.2 Hz, H-5), 2.92–2.79 (m, 1 H, H-2), 2.44 (ddd, *J* = 12.8, 9.5, 3.1 Hz, H-3), 2.01–1.93 (m, 1 H, H-3), 1.29 (d, *J* = 7.3 Hz, 3 H, CH_3), 1.05 (s, 9 H, *t*-Bu); MS *m*/*e* 369 (M + 1), 351, 348, 331, 311, 291. Anal. Calcd for $C_{22}H_{28}O_3Si$; C, 71.70; H, 7.66. Found: C, 71.66; H, 7.52.

(3*R*,5*S*)-Dimethyl [6-[(*tert*-Butyldiphenylsilyl)oxy]-3-methyl-2-oxo-5-(trimethylsiloxy)hexyl]phosphonate (6). To a solution of dimethyl methylphosphonate (1.54 mL, 14 mmol) in dry THF at −78 °C was added 1.55 M BuLi (9.2 mL, 14 mmol). After 25 min, a solution of lactone **5** (5 g, 13.6 mmol) in 8 mL of dry THF was added slowly. After 30 min, a solution of freshly prepared lithium diisopropylamide (1.55 M BuLi (8.8 mL, 13.6 mmol) and diisopropylamine (1.9 mL, 13.6 mmol)) in 20 mL of dry THF was added. The reaction mixture was allowed to warm to −20 °C and was held there for 30 min, at which time chlorotrimethylsilane (3.6 mL, 28 mmol) was added. The solution was stirred overnight and then allowed to warm gradually to room temperature. The reaction was quenched at 0 °C by the addition of saturated ammonium chloride solution (5 mL), followed by water (200 mL). The resulting solution was extracted four times with a total of 500 mL of diethyl ether, and the organic phase

(43) Hückel, W.; Tappe, W.; Legutke, G. *Ann. Chem.* **1940**, *543*, 191. Alexander, E. R.; Mudrak, A. *J. Am. Chem. Soc.* **1951**, *73*, 59. Briggs, W. S.; Djerassi, C. *J. Org. Chem.* **1968**, *33*, 1625.

(44) An identical strategy starting with (*S*)-4-(hydroxymethyl)-4-butanolide instead of **5** led to the tricyclic lactone corresponding to dihydrocompactin: Hanessian, S.; Hodges, P. J., unpublished results.

(45) The Chiron Program, Copyright, 1987. For examples of Chiron analyses, see: The Chiron Program Manual. See also: Hanessian, S. In *Organic Synthesis-An Interdisciplinary Challenge*; Streith, J., Prinsbach, H., Schill, G., Eds.; Blackwell: Boston, USA, 1985, 267. Hanessian, S.; Sakito, Y.; Dhanoa, D.; Baptistella, L.; *Tetrahedron* **1989**, *45*, 6623. Hanessian, S.; Faucher, A.-M.; Lēger, S. *Tetrahedron* **1990**, *46*, 231. Hanessian, S.; Franco, J.; Larouche, B. *Pure Appl. Chem.*, in press.

(46) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

was washed with deionized water (3 × 50 mL) and saturated sodium chloride solution (50 mL). The ether layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give a syrup, which was purified by flash chromatography. Elution was carried out with a gradient of 1:9 EtOAc–hexanes, 1:4 EtOAc–hexanes, and 1:2 EtOAc–hexanes to yield a colorless syrup (6.34 g, 83%): $[\alpha]^{25}_D$ −38.0° (*c* 2.0, $CHCl_3$); IR (film) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69–7.64 (m, 4 H, Ar), 7.44–7.39 (m, 6 H, Ar), 3.78 (d, 3 H, *J* = 3.7 Hz, OMe), 3.74 (d, 3 H, *J* = 3.7 Hz, OMe), 3.75–3.67 (m, 1 H, H-5), 3.57 (dd, 1 H, *J* = 10, 5.1 Hz, H-6), 3.47 (dd, 1 H, *J* = 10, 7.1 Hz, H-6), 3.33 (dd, 1 H, *J* = 23, 16.5 Hz, H-1), 3.00 (dd, 1 H, *J* = 23, 15 Hz, H-1), 2.90–2.80 (m, 1 H, H-3), 2.08 (ddd, 1 H, *J* = 14.3, 7.8, 4.0 Hz, H-4), 1.70 (ddd, 1 H, *J* = 14.3, 6.9, 4.3 Hz, H-4), 1.13 (d, 3 H, *J* = 6.9 Hz, C-3 Me), 1.06 (s, 9 H, *t*-Bu), −0.02 (s, 9 H, $SiMe_3$); MS *m/e* 507, 487, 428, 409, 396.

3-(Phenylseleno)butanal (7). To a suspension of diphenyl diselenide (12.48 g, 40 mmol) in 20 mL of absolute ethanol at 0 °C was added sodium borohydride (3.03 g, 80 mmol) in small portions. The clear pale yellow solution was then slowly transferred by a double-tipped needle to a stirring solution of freshly distilled crotonaldehyde (8.0 mL, 96 mmol) in absolute ethanol (400 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 40 min, at which point 1 M hydrochloric acid (50 mL) was added. The solution was diluted with deionized water (200 mL) and was then extracted three times with a total of 700 mL of diethyl ether. The ether layer was washed with 1 M hydrochloric acid (50 mL), saturated sodium bicarbonate solution (50 mL), deionized water (2 × 10 mL), and saturated sodium chloride solution (50 mL). The organic phase was then dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum to give a yellow residue, which was purified by flash column chromatography. Elution was carried out with hexanes to remove the diphenyl diselenide, followed by 1:20 EtOAc–hexanes and 1:9 EtOAc–hexanes to give a pale yellow oil (13.3 g, 73%). This reagent is best prepared immediately before use: ^1H NMR (400 MHz) δ (ppm) 9.69 (t, 1 H, *J* = 1.8 Hz, CHO), 7.6–7.53 (m, 2 H, Ar), 7.34–7.24 (m, 3 H, Ar), 3.69 (app sextet, 1 H, *J* = 6.8 Hz, H-3), 2.74 (ddd, 1 H, *J* = 17.2, 6.8, 1.2 Hz, H-2), 2.68 (ddd, *J* = 17.2, 6.8, 1.2 Hz, H-2), 1.46 (d, 3 H, *J* = 6.8 Hz, H-4).

(2*S*,4*R*,6*E*,8*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-4-methyl-2-[(trimethylsilyl)oxy]-6,8-decadien-5-one (8). To a suspension of 60% sodium hydride (0.54 g, 13.5 mmol) in 20 mL of dry THF at 0 °C was added a solution of phosphonate **6** (6.34 g, 11.2 mmol) in 20 mL of dry THF. After being stirred for 30 min, a solution of 3-(phenylseneo)butanal (**7**) (3.06 g, 13.5 mmol) in 20 mL of dry THF was added. One hour later, a saturated ammonium chloride solution (5 mL) was added and the mixture was diluted with 150 mL of water and extracted with a total of 400 mL of diethyl ether. The ether layer was washed with deionized water (3 × 75 mL) and saturated sodium chloride solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated to give a yellow syrup, which was purified by flash column chromatography, eluting first with hexanes, followed by 1:20 EtOAc–hexanes. The purified intermediate (6.7 g) was dissolved in 60 mL of dichloromethane at 0 °C, and 30% hydrogen peroxide (10 mL) was added with vigorous stirring. After 20 min, saturated sodium bicarbonate solution (20 mL) was added, and the two-phase system was extracted with 400 mL of diethyl ether. The organic phase was washed with deionized water (3 × 50 mL) and saturates sodium chloride solution (50 mL). After being dried over anhydrous sodium sulfate, the solvent was removed under vacuum and the residue was purified by flash chromatography (1:20 EtOAc–hexanes) to give a pale yellow syrup (4.7 g, 82%): $[\alpha]^{25}_D$ −27.6° (*c* 2.1, $CHCl_3$); IR (film) 1690, 1660, 1640, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70–7.66 (m, 4 H, Ar), 7.43–7.14 (m, 6 H, Ar), 7.21–7.14 (m, 1 H, H-7), 6.25–6.10 (m, 3 H, H-6, H-8, H-9), 3.75–3.65 (m, 1 H, H-2), 3.55 (dd, 1 H, *J* = 10.2, 5.2 Hz, H-1), 3.47 (dd, 1 H, *J* = 10.3, 6.4 Hz, H-1′), 2.97–2.88 (m, 1 H, H-4), 2.16 (ddd, 1 H, *J* = 13.8, 9.2, 3.7 Hz, H-3), 1.87–1.86 (m, 3 H, C-9 Me), 1.44 (ddd, 1 H, *J* = 13.8, 8.2, 4.5 Hz, H-3′), 1.12 (d, 3 H, *J* = 6.8 Hz, C-4 Me), 1.06 (s, 9 H, *t*-Bu), −0.02 (s, 9 H, $SiMe_3$). Anal. Calcd for $C_{30}H_{44}O_3Si_2$: C, 70.89; H, 8.72. Found: C, 70.56; H, 8.51.

(2*S*,4*R*,5*S*,6*E*,8*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-4-methyl-2-[(trimethylsilyl)oxy]-6,8-decadien-5-ol (9). A solution of **8** (4.7 g, 9.2 mmol) in 28 mL of dry THF was cooled to −78 °C under an argon stream, and 1.0 M L-Selectride solution in THF (9.7 mL, 9.7 mmol) was added over a period of 15 min. After stirring for a further 25 minutes, the reaction was quenched by the addition of saturated ammonium chloride solution (10 mL). Water (150 mL) was then added and the solution was extracted with a total of 400 mL of diethyl ether. The organic phase was washed with deionized water (3 × 50 mL) and saturated sodium chloride solution (50 mL) and then dried over anhydrous sodium sulfate. Evaporation under vacuum gave a syrup, which was purified by flash chromatography on silica gal (1:20 EtOAc–hexanes) to give a colorless oil (2.91 g, 62%): $[\alpha]^{25}_D$ −16.5° (*c* 2.15, $CHCl_3$); IR (film) 3420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67–7.65 (m, 4 H, Ar), 7.45–7.36 (m, 6 H, Ar), 6.16 (dd, 1 H, *J* = 15.1, 10.4 Hz, H-7), 6.08–6.01 (m, 1 H, H-6), 5.71–5.65 (m, 1 H, H-9), 5.53 (dd, 1 H, *J* = 15.2, 7.2 Hz, H-8), 3.90–3.83 (m, 1 H, H-2), 3.59–3.47 (m, 2 H, H-1), 2.62 (d, 1 H, *J* = 3.4 Hz, H-5), 1.80–1.74 (m, 4 H, H-4, C-9 Me), 1.55–1.45 (m, 2 H, H-3), 1.05 (s, 9 H, *t*-Bu), 0.05 (s, 9 H, $SiMe_3$); MS *m/e* 403 (100), 237, 147, 121.

(2*S*,4*R*,5*S*,6*E*,8*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-5-(methoxymethoxy)-4-methyl-2-[(trimethylsilyl)oxy]-6,8-decadiene (10). A solution of diisopropylethylamine (7 mL, 40 mmol) in 10 mL of dry dichloromethane was cooled to 0 °C, and chloromethyl methyl ether 3.05 mL, 40 mmol) was added slowly, under argon flow. The resulting solution was then transferred by double-tipped needle to a flask containing a solution of alcohol **9** (4.1 g, 8 mmol) and diisopropylethylamine (7 mL, 40 mmol) in dry dichloromethane (5 mL) at 0 °C. Dimethylaminopyridine (98 mg, 0.8 mmol) was then added, and the ice bath was removed. After being stirred for 3 h at room temperature, the solution was recooled to 0 °C and water (10 mL) and diethyl ether (25 mL) were added. The mixture was then further diluted with 50 mL of water and was extracted three times with a total of 400 mL of diethyl ether. The combined extracts were washed with deionized water (3 × 50 mL) and saturated sodium chloride solution (50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to give a syrup, which was purified by flash chromatography (1:20 EtOAc–hexanes). The product was obtained as a colorless oil (3.8 g, 85%): $[\alpha]^{25}_D$ +29.0° (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70–7.66 (m, 4 H, Ar), 7.43–7.34 (m, 6 H, Ar), 6.18–6.00 (m, 2 H, H-7, H-6), 5.73–5.63 (m, 1 H, H-9), 5.36 (dd, 1 H, *J* = 14.8, 8.4 Hz, H-8), 4.69 (d, 1 H, *J* = 6.8 Hz, O-CH_2-O), 4.49 (d, 1 H, *J* = 6.6 Hz, O-CH_2-O), 3.91–3.81 (m, 2 H, H-2, H-5), 3.58–3.43 (m, 2 H, H-1), 3.34 (s, 3 H, OMe), 1.90–1.79 (m, 2 H, H-3, H-4), 1.26–1.12 (m, 1 H, H-3), 1.04 (s, 9 H, *t*-Bu), 0.92 (d, 3 H, *J* = 6.6 Hz, C-4 Me), 0.08 (s, 9 H, $SiMe_3$); MS *m/e* 554 (M + 1), 509, 493, 465, 403, 237, 147, 121. Anal. Calcd for $C_{32}H_5O_4Si_2$: C, 69.26; H, 9.08. Found: C, 68.92; H, 8.88.

(2*S*,4*R*,5*S*,6*E*,8*E*)-5-(Methoxymethoxy)-4-methyl-6,8-decadiene-1,2-diol (11). To a solution of **10** (6.26 g, 11.3 mmol) in 25 mL of THF at 0 °C was added 1 M tetrabutylammonium fluoride solution in THF (25 mL, 25 mmol). The ice bath was removed and the pale brown solution was stirred for 2 h at room temperature. The solvent was then removed under vacuum and the residue was applied directly to a column of flash silica gel. Elution was effected with 1:4 EtOAc–Hexanes, followed by 2:1 EtOAc–hexanes, to afford the desired product as a colorless oil (2.69 g, 98%): $[\alpha]^{25}_D$ +92.4° (*c*, 2.5, $CHCl_3$); IR (film) 3700–3100, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.17–5.98 (m, 2 H, H-7, H-6), 5.76–5.68 (m, 1 H, H-9), 5.37 (dd, 1 H, *J* = 14.8, 8.4 Hz, H-8), 4.71 d, 1 H, *J* = 6.7 Hz, O-CH_2-O), 4.51 (d, 1 H, *J* = 6.7 Hz, O-CH_2-O), 3.91–3.84 (m, 2 H, H-2, H-5), 3.63–3.59 (m, 1 H, H-1), 3.47–3.42 (m, 1 H, H-1′), 3.38 (s, 3 H, OMe), 1.90–1.83 (m, 1 H, H-4), 1.76 (d, 3 H, *J* = 6.7 Hz, C-9 Me), 1.62–1.55 (m, 1 H, H-3), 1.52–1.44 (m, 1 H, H-3′), 0.97 (d, 3 H, *J* = 6.7 Hz, C-4 Me); MS *m/e* 183, 182, 165, 147, 141.

(2*S*,4*R*,5*S*,6*E*,8*E*)-1-[[(2′,4′,6′-Triisopropylphenyl)-sulfonyl]oxy]-5-(methoxymethoxy)-4-methyl-6,8-decadien-2-ol (12). To a solution of diol **11** (4.44 g, 18 mmol) in 35 mL of dry dichloromethane and 35 mL of dry pyridine at 0 °C was added triisopropylbenzenesulfonyl chloride (6.8 g, 22 mmol). The yellow solution was stirred at −5 °C for 2 days. A further portion of the sulfonylating agent (1 g) was then added, and the solution was stirred for an additional 16 h at −5 °C. Water (50 mL) was

then added and the solution was extracted three times with a total of 500 mL of diethyl ether. After washing with saturated copper(II) sulfate solution (5 × 50 mL) and deionized water (2 × 50 mL), the organic layer wad dried over anhydrous sodium sulfate and evaporated to give a pale blue syrup. The crude product was purified by flash chromatography, eluting with 1:9 EtOAc–hexanes followed by 1:4 EtOAc–hexanes to give a colorless syrup (6.95 g, 75%): $[\alpha]^{25}_D$ +52.4° (*c* 2.4, $CHCl_3$); IR (film) 3550, 3450, 1665, 1605, 1565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.19 (s, 2 H, Ar), 6.15–6.00 (m, 2 H, H-7, H-6), 5.75–5.66 (m, 1 H, H-9), 5.32 (dd, 1 H, *J* = 14.8, 8.4 Hz, H-8), 4.68 (d, 1 H, *J* = 6.8 Hz, O-CH_2-O), 4.47 (d, 1 H, *J* = 6.8 Hz, O-CH_2-O), 4.19, 4.10 (m, 2 H, C-2′, C-6′ isopropyl methine), 4.09–4.00 (m, 2 H, H-2, H-5), 3.94–3.89 (m, 1 H, H-1), 3.84 (dd, 1 H, *J* = 8.4, 6.4 Hz, H-1′), 3.34 (s, 3 H, OMe), 2.96–2.85 (m, 1 H, C-4′ isopropyl methine), 1.90–1.81 (m, 1 H, H-4), 1.69–1.60 (m, 1 H, H-3), 1.54–1.44 (m, 1 H, H-3′), 1.26 (d, 12 H, *J* = 6.6 Hz, isopropyl Me), 0.94 (d, 3 H, *J* = 6.6 Hz, C-4 Me); MS *m/e* 449 (100) 437, 381, 165.

(2*S*,4*R*,5*S*,6*E*,8*E*)-1,2-Epoxy-5-(methoxymethoxy)-4-methyl-6,8-decadiene (13). A solution of the sulfonate **12** (6.95 g, 136 mmol) in 45 mL of dry dichloromethane was cooled to 0 °C, and 1 M sodium methoxide/methanol (16 mL, 16 mmol) was added slowly. After being stirred for 40 min, the solution was diluted with 100 mL of water and extracted three times with a total of 300 mL of diethyl ether. The organic phase was washed with 1% sodium chloride solution (4 × 30 mL), followed by saturated sodium chloride solution (30 mL). The solvent was removed under vacuum, and the residue was purified by flash chromatograph (1:9 EtOAc–hexanes) to give a colorless oil (2.68 g, 87%): $[\alpha]^{25}_D$ +106.4° (*c* 2.35, $CHCl_3$); IR (film) 1665, 1455, 1415, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.18–6.02 (m, 2 H, H-7, H-6), 5.76–5.67 (m, 1 H, H-9), 5.35 (dd, 1 H, *J* = 15.2, 8.8 Hz, H-8), 4.70 (d, 1 H, *J* = 6.6 Hz, O-CH_2-O), 4.49 (d, 1 H, *J* = 6.6 Hz, O-CH_2-O), 3.83 (dd, 1 H, *J* = 8.5, 6.6 Hz, H-5), 3.36 (s, 3 H, OMe), 3.00–2.95 (m, 1 H, H-2), 2.76–2.73 (m, 1 H, H-1), 2.44 (dd, 1 H, *J* = 5.2, 2.8 Hz, H-1′), 1.94–1.78 (m, 2 H, H-4, H-3), 1.76 (dd, 3 H, *J* = 6.9, 1.4 Hz, C-9 Me), 1.39–1.32 (m, 1 H, H-3′), 1.01 (d, 3 H, *J* = 6.9 Hz, C-4 Me); MS *m/e* 227 (M + 1), 195, 181, 164, 147, 141. Anal. Calcd for $C_{13}H_{23}O_{31}$: C, 68.99; H, 9.80. Found: C, 68.73; H, 9.61.

(2*Z*,4*S*,6*R*,7*S*,8*E*,10*E*)-7-(Methoxymethoxy)-6-methyl-2,8,10-dodecatrien-1,4-olide (14). To a solution of diisopropylamine (3.23 mL, 23 mmol) in 35 mL of dry THF at 0 °C was added slowly a 1.5 M BuLi solution (15.4 mL, 23 mmol) with stirring. The solution was then cooled to −15 °C and a solution of (phenylselenenyl)acetic acid (2.48 g, 11.5 mmol) in 9 mL of dry THF was added slowly. The resulting pale yellow solution was stirred for 15 min and then transferred to a flask containing epoxide **13** (1.74 g, 7.7 mmol) in 9 ml of dry THF at −15 °C. The flask was covered with aluminum foil, and the solution was allowed to warm to room temperature. After 23 h, TLC (1:4 EtOAc–hexanes) indicated that the epoxide had been consumed. The reaction mixture was cooled to 0 °C, and 6 M hydrochloric acid (24 mL) was slowly added. The solution was further diluted with water (50 mL) and extracted four times with a total of 450 mL of diethyl ether. The organic layer was washed with saturated sodium chloride solution (3 × 40 mL) and then evaporated to dryness. The residue was dried under vacuum (0.1 mmHg) for 1 h and dissolved in 40 mL of dry dichloromethane. The solution was cooled to 0 °C, and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (1.62 g, 8.5 mmol) was added. After 3 h at room temperature, 25 mL of water was added, and the aqueous phase was extracted with a total of 300 mL of diethyl ether. The ether layer was washed with saturated sodium chloride solution (3 × 50 mL) and evaporated to yield a pale yellow residue, which was purified by flash chromatography (1:4 EtOAc–hexanes). The resulting phenylselenenyl lactone (3 g) was dissolved in 30 mL of dichloromethane at 0 °C, and 30% hydrogen peroxide (10 mL) was added with vigorous stirring. After 30 min, saturated sodium bicarbonate solution (10 mL) was added, and the two-phase system was extracted with 200 mL of diethyl ether. The ether layer was washed with deionized water (3 × 30 mL) and saturated sodium chloride solution (30 mL). After evaporation, the crude product was purified by flash chromatography (1:4 EtOAc–hexanes) to give a colorless syrup (1.44 g, 70%): $[\alpha]^{25}_D$ +149° (*c* 1.9, $CHCl_3$); IR (film) 1765, 1665, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48 (dd, 1 H, *J* = 5.6, 1.6 Hz, H-3), 6.19–6.01 (m, 3 H, H-9, H-2, H-3′), 5.78–5.69 (m, 1 H, H-11), 5.32 (dd, 1 H, *J* = 15.2, 8.6 Hz, H-10), 5.18–5.13 (m, 1 H, H-4), 4.69 (d, 1 H, *J* = 6.7 Hz, O-CH_2-O), 4.48 (d, 1 H, *J* = 6.7 Hz, O-CH_2-O), 3.83 (dd, 1 H, *J* = 8.8, 6.7 Hz, H-7), 3.35 (s, 3 H, OMe), 2.01–1.85 (m, 2 H, H-6, H-5), 1.76 (d, 3 H, *J* = 6.7 Hz, C-11 Me), 1.59–1.49 (m, 1 H, H-5′), 1.01 (d, 3 H, *J* = 7.0 Hz, C-6 Me); MS *m/e* 205, 187, 159, 141, 109.

(1*R*,2*S*,4a*R*,5*S*,6*R*,8*S*,8a*S*)-1-Carboxy-5-(methoxymethoxy)-2,6-dimethyl-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene 1,8-Lactone (15). A solution of **14** (2.11 g, 7.9 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (20 mg) in 85 mL of distilled *o*-xylene was brought to reflux under an argon atmosphere. After 6 days, the solution was concentrated under vacuum and the residue was applied directly to a column of flash silica gel. Elution was carried out with 1:9 EtOAc–hexanes followed by 1:2 EtOAc–hexanes to give 1.57 g of yellow crystalline product, which was recrystallized from 24 mL of hexanes to give white prisms (1.38 g, 65%): mp 79–80 °C; $[\alpha]^{25}_D$ 10.1° (*c* 2.0, $CHCl_3$); IR (solution in CCl_4) 1780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.03 (ddd, 1 H, *J* = 9.6, 2.8, 2.2 Hz, H-3), 5.63 (dt, 1 H, *J* = 12.0, 2.4 Hz, H-4), 4.74 (d, 1 H, *J* = 6.9 Hz, O-CH_2-O), 4.66 (d, 1 H, *J* = 7.0 Hz, O-CH_2-O), 4.56–4.51 (m, 1 H, H-8), 3.62–3.57 (m, 1 H, H-5), 2.61–2.54 (m, 1 H, H-2), 2.46–2.43 (m, 1 H, H-1), 2.15–1.87 (m, 5 H, H-4a, H-6, H-7, H-8a), 1.25 (d, 3 H, *J* = 7.4 Hz, C-2 Me), 1.05 (d, 3 H, *J* = 6.9 Hz, C-6 Me); Me *m/e* 267 nM + 1), 205, 161, 159, 105. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32. Found: C, 67.61; H, 8.11.

(1*R*,2*S*,4a*R*,5*S*,6*R*,8*S*,8a*S*)-1-Carboxy-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-5,8-diol 1,8-Lactone (16). To a solution of **15** (1.33 g, 4.96 mmol) in 60 mL of THF was added 6 M hydrochloric acid (4 mL). The resulting solution was stirred at 40 °C for 19 h, at which point TLC (1:2 EtOAc–hexanes) indicated that the starting material had been consumed. The reaction mixture was cooled to 0 °C, and 25 mL of saturated sodium bicarbonate solution was carefully added. The solution was then concentrated on the rotary evaporator, and the residual aqueous phase was extracted four times with a total of 250 mL of diethyl ether. The organic phase was washed with water (25 mL) and saturated sodium chloride solution (25 mL). After removal of the solvent under vacuum, the crude product was purified by flash chromatography, eluting with 1:9 EtOAc–hexanes followed by 1:2 EtOAc–hexanes, to give a white solid (1.05 g, 95%): mp 107–107.5 °C; $[\alpha]^{25}_D$ +53.5° (*c* 2.03, $CHCl_3$); IR (Nujol mull) 3620, 3500, 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.9 (ddd, 1 H, *J* = 9.7, 2.7, 2.6 Hz, H-3), 5.64 (ddd, 1 H, *J* = 9.6, 2.8, 2.5 Hz, H-4), 4.62–4.56 (m, 1 H, H-8), 3.73–3.66 (m, 1 H, H-5), 2.63–2.52 (m, 1 H, H-2), 2.46 (dd, 1 H, *J* = 7.5, 2.5 Hz, H-1), 2.04–1.77 (m, 5 H, H-a, H-6, H-7, H-8a), 1.54 (d, 1 H, *J* = 7.2 Hz, OH), 1.24 (d, 3 H, *J* = 7.5 Hz, C-2 Me), 1.07–1.05 (m, 3 H, Ch-6 Me); MS *m/e* calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1250; CIMS *m/e* 223 (M + 1), 205, 159, 105. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 7.87.

(1*R*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-Carboxy-2,6-dimethoxy-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene 1,8-Lactone (18). To a suspension of 60% sodium hydride (42 mg, 1.05 mmol) and one crystal of imidazole in 2.5 mL of dry THF at 0 °C was added alcohol **16** (222 mg, 1 mmol). After several minutes, carbon disulfide (0.18 mL, 3 mmol) was added followed by iodomethane (0.12 mL, 2 mmol). The resulting yellow solution was stirred at 0 °C for 2 h, at which point TLC (1:2 EtOAc–hexanes) indicated the presence of a small amount of starting material. A second portion of sodium hydride (10 mg) was added, and the reaction mixture was stirred for an additional 2 h at 0 °C. Saturated ammonium chloride solution (2 mL) was then added, followed by water (5 mL), and the solution was extracted twice with a total of 70 mL of diethyl ether. The organic layer was washed with deionized water (3 × 5 mL) and saturated sodium chloride solution (5 mL). After removal of the solvent, the crude xanthate **17** was purified on a short column of flash silica gel, eluting with 1:9 EtOAc–hexanes and 1:4 EtOAc–hexanes. The resulting yellow syrup (0.25 g) was dissolved in toluene (30 mL) and treated with tributyltin hydride (0.26 mL, 1 mmol) and several crystals of AIBN. After being heated at reflux for 35 min, the reaction mixture was cooled to room temperature and concentrated to dryness under vacuum. The residue was purified by flash

chromatography, eluting with hexanes until all of the tin byproducts had been removed, followed by 1:9 EtOAc–hexanes and 1:4 EtOAc–hexanes. The product was obtained as a white crystalline solid (140 mg, 68%): mp 75.5–77 °C; $[\alpha]^{25}_D$ +121.6° (*c* 2.0, $CHCl_3$); IR (solution in CCl_4) 1775, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.65–5.61 (m, 1 H, H-3), 5.58–5.54 (m, 1 H, H-4), 4.68–4.63 (m, 1 H, H-8), 2.58–2.50 (m, 1 H, H-2), 2.45 (dd, 1 H, *J* = 7.4, 3.8 Hz, H-1), 2.01 (m, 1 H), 1.96–1.87 (m, 2 H), 1.86–1.75 (m, 1 H), 1.63–1.48 (m, 3 H), 1.25 (d, 3 H, *J* = 7.4 Hz, C-2 Me), 1.04 (d, 3 H, *J* = 6.9 Hz, C-6 Me); MS *m/e* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1313; CIMS *m/e* 207 (M + 1), 189, 161, 105.

(1*R*,2*S*,6*R*,8*S*,8a*R*)-1-Carboxy-2,6-dimethyl-8-hydroxy-1,2,6,7,8,8a-hexahydronaphthalene 1,8-Lactone (39). A solution of xanthate **17** (21 mg, 0.07 mmol) in distilled *o*-xylene was brought to reflux under an argon atmosphere. After 6 h, TLC (1:4 Et_2O/hexanes) indicated that the starting material had been consumed. The solvent was removed under vacuum, and the residue was applied directly to a column of flash silica gel. Elution with 1:4 Et_2O/hexanes gave diene **39** as a colorless oil (11 mg, 80%); $[\alpha]^{25}_D$ +288.6° (*c* 1.1, $CHCl_3$); IR (film) 1770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.06 (d, 1 H, *J* = 9.9 Hz, H-5), 5,68 (t, 1 H, *J* = 2.9 Hz, H-3), 5.62 (dd, 1 H, *J* = 10.1, 4.8 Hz, H-4), 4.80–4.75 (m, 1 H, H-8), 2.90–2.80 (m, 2 H, H-2, H-8a), 2.70 (d, 1 H, *J* = 7.5 Hz, H-1), 2.37–2.29 (m, 1 H, H-6), 2.29–2.20 (m, 1 H, H-7 eq), 1.67 (ddd, 1 H, *J* = 12.3, 7.0, 3.9 Hz, H-7ax), 1.19 (d, 3 H, *J* = 7.3 Hz, C-2 Me), 1.12 (d, 3 H, *J* = 7.1 Hz, C-6, Me); MS *m/e* 205 (M + 1), 159, 135, 121, 105, 93.

(1*R*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-2,6-Dimethyl-1-(hydroxymethyl)-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene (19). To a solution of lactone **18** (398 mg, 1.9 mmol) in 8 mL of dry THF at 0 °C was added dropwise a 1 M solution of lithium aluminum hydride in THF (1.45 mL, 1.45 mmol). After 30 min, the reaction was quenched by the addition of ethyl acetate (1 mL), followed by water (1 mL) and 1 M hydrochloric acid (2 mL). The THF was then removed under vacuum and the aqueous residue was extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with deionized water (3 × 10 mL) and saturated sodium chloride solution (10 mL). After removal of the solvent, the crude diol was purified by flash chromatography, eluting first with 1:9 EtOAc–hexanes followed by 1:4 EtOAc–hexanes. A white crystalline solid was obtained (383 mg, 94%): mp 109–109.5 °C; $[\alpha]^{25}_D$ +138.3° (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.49 (dd, 1 H, *J* = 10.0, 5.0, 2.1 Hz, H-3), 5.35 (app d, 1 H, *J* = 9.7 Hz, H-4), 4.16 (br s, 2 H, OH), 4.04–4.01 (m, 1 H, H-8), 3.80 (t, 1 H, *J* = 11.3 Hz, CH_2OH), 3.39 (dd, 1 H, *J* = 11.4, 2.6 Hz, CH_2OH), 2.63–2.55 (m, 1 H, H-2), 2.10–1.98 (m, 2 H), 1.84–1.65 (m, 4 H), 1.58–1.53 (m, 1 H), 1.31 (dd, 1 H, *J* = 12.8, 5.1 Hz), 1.26 (d, 3 H, *J* = 7.5 Hz, C-2 Me), 1.06 (d, 3 H, *J* = 7.2 Hz, C-6 Me), 1.05 (d, 3 H, *J* = 7.1 Hz, C-2 Me); MS *m/e* 253 (M + 1), 235, 193, 175.

(1*R*,2*R*,4a*R*,6*S*,8*S*,8a*S*)-1-(Acetoxymethyl)-2,6-dimethyl-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene (20). To a solution of diol **19** (195 mg, 0.93 mmol) in dry pyridine (1 mL) at 0 °C was added acetic anhydride (0.18 mL, 1.9 mmol). After several minutes the ice bath was removed and the solution was stirred for 15 h at room temperature. TLC (1:2 EtOAc–hexanes) then indicated the presence of a small amount of starting material. A second portion of acetic anhydride (0.045 mL, 0.48 mmol) was added, and the reaction was stirred for an additional 5 h. Deionized water (3 mL) was then added, and the solution was extracted four times with a total of 250 mL of diethyl ether. The organic layer was washed with 1 M hydrochloric acid (3 × 20 mL), deionized water (2 × 10 mL), and saturated sodium chloride solution (10 mL). After removal of the solvent, the product was purified by flash chromatography (1:20 EtOAc–hexanes, 1:9 EtOAc–hexanes) to give a colorless syrup (213 mg, 91%): $[\alpha]^{25}_D$ +94.1° (*c* 0.8, $CHCl_3$); IR (film) 3520, 1740 (shoulder), 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.54–5.48 (m, 1 H, H-3), 5.43 (app d, 1 H, *J* = 10.1 Hz, H-4), 4.75 (dd, 1 H, *J* = 11.1, 4.4 Hz, H-8), 4.09–4.05 (m, 1 H, CH_2OAc), 3.94 (dd, 1 H, *J* = 11.1, 8.1 Hz, CH_2OAc), 2.50–2.40 (m, 1 H, H-4a), 2.34–2.27 (m, 1 H, H-2), 2.11–2.02 (m, 1 H, H-6), 2.07 (s, 3 H, Ac), 1.80–1.64 (m, 4 H), 1.47–1.42 (m, 1 H), 1.29–1.20 (m, 4 H, H-5ax, C-6 Me), 1.05 (d, 3 H, *J* = 7.1 Hz, C-2 Me); MS *m/e* 253 (M + 1), 235, 193, 175.

(1*R*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(Acetoxymethyl)-8-[(*tert*-butyldimethylsilyl)oxy]-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene (21). To a solution of acetate **20** (130 mg, 0.52 mmol) and triethylamine (0.36 mL, 2.6 mmol) in dry dichloromethane (3 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.24 mL, 1 mmol). After 30 min at room temperature, deionized water (4 mL) was added, and the solution was extracted with 40 mL of diethyl ether. The organic phase was washed with deionized water (3 × 1 mL) followed by saturated sodium chloride solution. The solvent was evaporated, and the residue was purified by flash chromatography, eluting with 1:50 EtOAc–hexanes. A colorless syrup (160 mg, 85%) was obtained: $[\alpha]^{25}_D$ +48.4° (*c* 0.75, $CHCl_3$); IR (film) 1745, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.50–5.46 (m, 1 H, H-3), 5.44 (app d, 1 H, *J* = 10.1 Hz, H-4), 4.69 (dd, 1 H, *J* = 10.9, 2.7 Hz, H-8), 4.07–4.04 (m, 1 H, CH_2OAc), 4.00 (t, 1 H, *J* = 10.9 Hz, CH_2OAc), 2.42–2.27 (m, 2 H, H-4a, H-2), 2.06–1.96 (m, 1 H, H-6), 2.03 (s, 3 H, Ac), 1.76–1.60 (m, 4 H), 1.45–1.40 (m, 1 H, H-5eq), 1.23–1.14 (m, 1 H, H-5ax), 1.19 (d, 3 H, *J* = 7.6 Hz, C-6 Me), 1.05 (d, 3 H, *J* = 7.1 Hz, C-2 Me), 0.91 (s, 9 H, *t*-Bu), 0.09 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe); MS *m/e* 367, 310, 176, 235, 175.

(1*R*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-1-(hydroxymethyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalene (22). To a solution of **21** (300 mg, 0.82 mmol) in dry THF (9 mL) at 0 °C was added 1 M lithium aluminum hydride in THF (0.82 mL, 0.82 mmol). After 40 min, deionized water (2 drops from a pasteur pipette) was added, followed by 15% w/v sodium hydroxide solution (2 drops) and deionized water (3 drops). The suspension was then filtered through a bed a Celite to remove the aluminum salts, and the filter cake was washed several times with ethyl acetate. The filtrate was evaporated to dryness, and the residue was purified by flash column chromatography. Elution was carried out with 1:20 EtOAc–hexanes to yield a colorless syrup (239 mg, 90%), which crystallized on standing: mp 49–50 °C; $[\alpha]^{25}_D$ +95.3° (*c* 2.3, $CHCl_3$); IR (film) 3360 (br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.53–5.49 (m, 1 H, H-3), 5.42 (app d, 1 H, *J* = 9.8 Hz, H-4), 4.26 (dd, 1 H, *J* = 10.5, 4.0 Hz, CH_2OH), 2.48–2.40 (m, 1 H, H-2), 2.40–2.10 (m, 1 H, H-4a), 2.05–1.96 (m, 1 H, H-6), 1.73–1.54 (m, 5 H); 1.46–1.40 (m, 1 H), 1.27–1.16 (m, 4 H, including C-6 Me), 1.06 (d, 3 H, *J* = 7.2 Hz, C-2 Me), 0.94 (s, 9 H, *t*-Bu), 0.12 (s, 6 H, $SiMe_2$); MS *m/e* calcd for $C_{19}H_{36}O_2Si$ 324.2486, found 324.2432; CIMS *m/e* 325 (100) (M + 1), 193, 175.

(1*R*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxaldehyde (23). A solution of oxalyl chloride (27 μL, 0.3 mmol) in dry dichloromethane (0.5 mL) was cooled to −55 °C. To this solution was added slowly a solution of dry dimethyl sulfoxide (47 μL, 0.67 mmol) in dry dichloromethane (0.5 mL). The resulting mixture was stirred for 2 min at −55 °C, and the flask was then transferred to a bath at −10 °C. A solution of alcohol **22** (45 mg, 0.14 mmol) in dry dichloromethane (0.5 mL) was added by double-tipped needle, and the reaction mixture was stirred for an additional 20 min at −10 °C. Triethylamine (97 μL, 69 mmol) was then added, and the resulting suspension was stirred at −10 °C for 5 min, at which time deionized water (1 mL) was added. The solution was extracted with 100 mL of diethyl ether, and the organic phase was washed with deionized water (2 × 5 mL) and saturated sodium chloride solution (5 mL). After evaporation of the solvent, the product was purified by flash column chromatography (1:100 Et_2O/hexanes, 1:50 Et_2O/hexanes) to give 37.5 mg (84%) of a colorless oil, which crystallized on standing: mp 68–68.5 °C; $[\alpha]^{25}_D$ +54.5° (*c* 0.45, $CHCl_3$); IR (film) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.90 (d, 1 H, *J* = 4.4 Hz, CHO), 5.58 (ddd, 1 H, *J* = 10.0, 4.6, 2.3 Hz, H-3), 5.49 (app d, 1 H, *J* = 9.2 Hz, H-4), 4.04–3.98 (m, 1 H, H-8), 2.98–2.87 (m, 1 H, H-4a), 2.41–2.32 (m, 1 H, H-2), 2.12–2.08 (m, 1 H, H-1), 2.08–2.01 (m, 1 H, H-6), 1.80–1.66 (m, 2 H, H-7), 1.65–1.59 (m, 1 H, H-8a), 1.32 (td, 1 H, *J* = 12.7, 5.0 Hz), 1.24 (d, 3 H, *J* = 7.5 Hz, C-6 Me), 1.11 (d, 3 H, *J* = 7.1 Hz, C-2 Me), 0.89 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, SiMe), 0.00 (s, 3 H, SiMe); MS calcd for $C_{19}H_{34}O_2Si$ 322.2328, found 322.2298; CIMS *m/e* 323 (M + 1), 265, 191, 173, 163, 149, 133.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxaldehyde (24). A suspension of aldehyde **23** (76 mg, 0.24

mmol) and potassium carbonate (39 mg) in dry methanol (1 mL) was prepared in a thick-walled test tube that had a constriction near the opening. The solution was degassed by using a freeze–pump–thaw cycle with liquid nitrogen. After the third cycle, the tube was sealed under vacuum with an oxy-propane torch. The tube was suspended in an oil bath at 100 °C for 19 h and then allowed to cool to room temperature. The solution was frozen with liquid nitrogen and the tube was broken open. The reaction mixture was transferred to a round-bottomed flask with several washes of ether, and the solution was evaporated to dryness to give a residue, which was suspended in ethyl acetate and filtered through Celite. The filtrate was evaporated and the resulting syrup was purified by flash chromatography (1:4 toluene/hexanes, 1:1 toluene/hexanes) to give the starting aldehyde (30 mg, 40%) and **24** as a white crystalline solid (40 mg, 53%): mp 49.5–50 °C; $[\alpha]^{25}_D$ +144° (*c* 0.65, $CHCl_3$); IR (Nujol) 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.77 (d, 1 H, *J* = 2.3 Hz, CHO), 5.60 (ddd, 1 H, *J* = 9.9, 4.7, 2.7 Hz, H-3), 5.43 (app d, 1 H, *J* = 9.8 Hz, H-4), 4.34–4.32 (m, 1 H, H-8), 2.86 (ddd, 1 H, *J* = 11.4, 5.8, 2.3 Hz, H-1), 2.76–2.67 (m, 1 H, H-2), 2.57–2.48 (m, 1 H, H-4a), 2.07–1.98 (m, 1 H, H-6), 1.73–1.68 (m, 2 H), 1.68–1.60 (m, 1 H, 1.59–1.55 (m, 1 H), 1.38 (td, 1 H, *J* = 13.0, 5.3 Hz), 1.18 (d, 3 H, *J* = 7.5 Hz, C-6 Me), 0.92 (d, 3 H, *J* = 7.0 Hz, C-2 Me), 0.88 (s, 9 H, *t*-Bu), 0.07 (s, 3 H, Si-Me), −0.66 (s, 3 H, si-Me); MS *m/e* calcd for $C_{19}H_{24}O_2Si$ 322.2328, found 322.2333; CIMS *m/e* 323 (M + 1), 265, 233, 191 (100), 173, 163.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-2,6-Dimethyl-1-(hydroxymethyl)-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene (26). To a solution of aldehyde **24** (10 mg, 0.031 mmol) in methanol (0.5 mL) was added sodium borohydride (2 mg, 0.062 mmol). After 5 min, 1 M hydrochloric acid (2 drops) was added, and the solution was diluted with water (5 mL) and extracted three times with a total of 20 mL of diethyl ether. The organic phase was washed with saturated sodium chloride solution (1 mL) and was then dried over anhydrous sodium sulfate. The solution was filtered and concentrated under vacuum to give an oil, which was purified on a short column of flash silica gel (1:20, 1:9, 1:6 EtOAc–hexanes). The resulting alcohol (9.5 mg) was dissolved in a solution of 40% aqueous hydrofluoric acid/acetonitrile (5:95 v/v) (1 mL), and the mixture was stirred for 4 h. Saturated sodium bicarbonate solution (3 drops) was then added, and the mixture was extracted with 20 mL of dichloromethane. The organic phase was washed with deionized water (2 × 1 mL), followed by saturated sodium chloride solution (1 mL). The solvent was then removed under vacuum and the residue was purified by flash chromatography (1:4, 1:2 EtOAc–hexanes). The product was obtained as a white crystalline solid (5.9 mg, 91%): mp 114–155 °C; $[\alpha]^{25}_D$ +151.5° (*c* 0.59, $CHCl_3$), lit.[9] $[\alpha]_D$ +152° ($CHCl_3$)f ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.55 (ddd, 1 H, *J* = 9.7, 4.8, 2.6 Hz, H-3), 5.41–5.37 (m, 1 H, H-4), 4.25–4.21 (m, 1 H, H-8), 3.77 (t, 1 H, *J* = 9.9 Hz, CH_2OH), 3.67 (dd, 1 H, *J* = 9.9, 2.4 Hz, CH_2OH), 2.72 (br s, 2 H, 2 × OH), 2.56–2.45 (m, 1 H, H-4a), 2.43–2.34 (m, 1 H, H-2), 2.09–1.96 (m, 2 H, H-1, H-6), 1.87–1.72 (m, 2 H, H-7), 1.61–1.54 (m, 1 H, H-5eq), 1.31 (td, 1 H, *J* = 13.1, 51 Hz, H-5ax), 1.25–1.16 (m, 4 H, H-8a, C-6 Me), 0.81 (d, 3 H, *J* = 7.1 Hz, C-2 Me).

(1*R*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(2-Nitro-1-ethenyl)-2,6-dimethyl-8-[(*tert*-butyldimethylsilyl)oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (27). The aldehyde **24** (0.150 g, 0.465 mmol) was dissolved in 15 mL of dry methanol, and a solution of nitromethane (10 mL) in 5 mL of sodium methoxide (0.18 M) was added dropwise under argon. After being stirred at room temperature for 2 h, the solution was neutralized by adding glacial acetic acid. Evaporation of the solvent left a solid residue that was dissolved in dichloromethane (225 mL), the solution was filtered through a short Florisil pad, the filtrate was concentrated, and the residue was chromatographed, using EtOAc–hexanes (5:95) as eluent, to give 0.13 g (73%) of the nitro alcohol and 0.02 g of recovered aldehyde. The preceding compound (0.13 g, 0.338 mmol) was dissolved in 15 mL of dry dichloromethane, and the solution was cooled at 0 °C. Methanesulfonyl chloride (0.13 mL, 1.7 mmol) was added in one portion, followed by the addition of Et_3N (0.47 mL, 3.35 mmol). After stirring for 1 h at 0 °C under argon, the solvent was removed by concentration, and the residue was treated with ether and washed with a 5% solution of hydrochloric acid and then deionized water. Drying of the organic phase, evaporation of the solvent, and chromatography using EtOAc–hexanes (2:78) gave the title compound **27** (0.105 g, 85%) as a syrup; $[\alpha]^{25}_D$ +148.48° (*c* 0.165, $CHCl_3$); IR (film) 1640, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (dd, 1 H, *J* = 13.5 Hz), 6.98 (d, 1 H, *J* = 13.5 Hz), 5.64–5.58 (m, 1 H), 5.47–5.43 (m, 1 H), 3.93–3.90 (m, 1 H), 2.80–2.68 (m, 1 H), 2.62–2.50 (m, 1 H), 2.38–2.25 (m, 1 H), 2.10–1.96 (m, 1 H), 1.82–1.74 (m, 1 H), 1.66–1.56 (m, 1 H), 1.44–1.25 (m, 1 H), 1.18 (d, 3 H, *J* = 7.1 Hz), 0.95 (d, 3 H, *J* = 7.1 Hz), 0.89 (s, 9 H), 0.09 (s, 3 H), −0.14 (s, 3 H); MS *m/e* 348, 308, 306, 234, 216, 187, 173.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(2-Nitroethyl)-2,6-dimethyl-8-[(*tert*-butyldimethylsilyl)oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (28). Nitroolefin **27** (0.1 g, 0.285 mmol) was dissolved in a mixture of 0.5 mL of 2-propanol and 13.5 mL of $CHCl_3$ and then treated with $NaBH_4$ (0.215 g, 0.55 mmol, added in one portion). Stirring was continued for 40 min and the excess reagent was destroyed with 10% hydrochloric acid. The solvent was evaporated, ether was added to the residue, and the ethereal solution was washed with brine and dried over $MgSO_4$. After evaporation of the solvent the residue was chromatrographed, using EtOAc–hexanes (2:98), to give **28** (0.095 g, 90%); $[\alpha]^{25}_D$ +143.83° (*c* 0.23, $CHCl_3$); IR (film) 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.64–5.55 (m, 1 H), 5.45–5.35 (m, 1 H), 4.52–4.40 (m, 1 H), 4.27–4.18 (m, 1 H), 4.14–4.08 (m, 1 H), 2.57–2.47 (m, 1 H), 2.43–2.32 (m, 1 H), 2.19–2.10 (m, 1 H), 2.06–1.95 (m, 1 H), 1.90–1.75 (m, 2 H), 1.66–1.52 (m, 2 H), 1.37–1.23 (m, 2 H), 1.17 (d, 3 H, *J* = 7.4 Hz), 1.18–1.04 (m, 1 H), 0.91 (d, 3 H, *J* = 7.0 Hz), 0.90 (s, 9 H), 0.14 (s, 3 H), 0.12 (s, 3 H); MS *m/e* 350, 317, 310, 292, 279, 236, 219, 189, 187.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(2-Nitroethyl)-2,6-dimethyl-8-hydroxy-1,2,4a,5,6,7,8,8a-octahydronaphthalene (29). The previous compound **28** (0.09 g, 0.26 mml) was treated with 10 mL of a mixture 4:1 of acetontrile and aqueous HF in a polyethylene flask. After 24 h at room temperature, the solvent was evaporated, the residue was dissolved in dichloromethane, and it was processed in the usual manner. Chromatography using EtOAc–hexanes (1:9) gave the title compound (0.06 g, 93%): mp 102–103 °C; $[\alpha]^{25}_D$ +135.5° (*c* 0.158 $CHCl_3$); IR (film) 3580, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.66–5.56 (m, 1 H), 4.43–4.34 (m, 1 H), 4.56–4.37 (m, 2 H), 4.17–4.10 (m, 1 H), 2.55–2.38 (m, 2 H), 2.30–2.20 (m, 1 H), 2.10–1.99 (m, 1 H), 1.92–1.71 (m, 4 H), 1.62–1.53 (m, 2 H), 1.35–1.22 (m, 2 H), 1.21 (d, 3 H, *J* = 7.5 Hz), 0.90 (d, 3 H, *J* = 7.0 Hz); MS *m/e* 253, 236, 189, 187, 157.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(2-Nitroethyl)-2,6-dimethyl-8-[[(*S*)-2-methyl-1-oxobutyl]oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (30). The preceding compound **29** (0.05 g, 0.195 mmol) was treated with 0.25 mL of (*S*)-2-methylbutyric anhydride and 5 mg of DMAP. The mixture was stirred at 40 °C for 20 min and then directly charged on a silica gel column. Elution with EtOAc–hexanes (1:7) gave **30** (0.046 g, 70%): mp 68–70 °C; $[\alpha]^{25}_D$ +116.3° (*c* 0.27, $CHCl_3$); IR (film) 1735, 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.67–5.60 (m, 1 H), 5.45–5.37 (m, 1 H), 5.17–5.15 (m, 1 H), 4.45–4.38 (m, 1 H), 4.35–4.27 (m, 1 H), 2.57–2.44 (m, 1 H), 2.38 (q, 1 H, *J* = 7.0 Hz), 2.34–2.24 (m, 1 H), 2.23–2.00 (m, 2 H), 1.99–1.89 (m, 1 H), 1.88–1.61 (m, 5 H), 1.60–1.43 (m, 2 H), 1.42–1.20 (m, 2 H), 1.15 (d, 3 H, *J* = 7.0 Hz), 1.10 (d, 3 H, *J* = 7.5 Hz), 0.93 (t, 3 H, *J* = 7.4 Hz), 0.88 (d, 3 H, *J* = 7.1 Hz); MS *m/e* 338, 306, 236, 202, 187, 103.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-[2-Nitro-2-[3(*S*)-[4(*R*)-[[*tert*-butyldimethylsilyl]oxy]-1-oxo-3-cyclopentyl]]ethyl]-2,6-dimethyl-8-[[(*S*)-2-methylbutyryl]oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (32). The ester derivative **30** (0.05 g, 0.15 mmol) dissolved in 0.5 mL of ether and (*R*)-4-(*tert*-butyldimethylsilyl)oxy]cyclopenten-1-one (**31**)[29] (0.05 g, 0.25 mmol) was added followed by 0.5 g of Amberlyst A-21. The solid mixture was left standing for 2 h and then diluted with ether, and the solvent was decanted (7 × 15 mL). The ethereal solution was filtered through a short Florisil pad, the solvent was removed, and the residue was chromatographed, using EtOAc–hexanes (1:3), to give **32** (0.06 g, 70%), which was used as such.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-[2-[3(*R*)-[4(*R*)-[[*tert*-Butyldimethylsilyl]oxy]-1-oxo-3-cyclopentyl]]ethyl]-2,6-dimethyl-8-[[(*S*)-2-methyl-1-oxobutyl]oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (33). The preceding compound **32** (0.06 g, 0.11 mmol) was dissolved in 15 mL of dry toluene, and the solution was treated with azobis(isobutyronitrile) (0.01 g) and *n*-tributyltin

hydride (0.09 mL, 0.325 mmol). After heating at reflux for 30 min, the solvent was evaporated, and the residue was directly chromatographed, using EtOAc–hexanes (2:3), to give **33** (0.03 g, 55%): $[\alpha]^{25}_D$ +46.25° (*c* 0.68, $CHCl_3$); IR (film); 1750, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.69–5.62 (m, 1 H), 5.42–5.37 (m, 1 H), 5.19–5.13 (m, 1 H), 4.04–3.96 (m, 1 H), 2.64–2.41 (m, 2 H), 2.32 (o, 1 H, *J* = 7.0 Hz), 2.27–1.22 (m, 18 H), 1.13 (d, 3 H, *J* = 7.0 Hz), 1.09 (d, 3 H, *J* = 7.5 Hz), 0.89 (t, 3 H, *J* = 7.5 Hz), 0.88 (s, 9 H), 0.83 (d, 3 H, *J* = 7.0 Hz), 0.08 (s, 3 H), 0.05 (s, 3 H); MS *m/e* (M + 1) 506, 403, 271, 173, 159, 103.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-[2-[3(*R*)-[4(*R*)-[[*tert*-Butyldimethylsilyl]oxy]-1(*R*)-hydroxy-3-cyclopentyl]]ethyl]-2,6-dimethyl-8-[[(*S*)-2-methyl-1-oxobutyl]oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (34). Compound **33** (0.053 g, 0.105 mmol) was dissolved in a mixture of 2.5 mL of 2-propanol and 10 mL of THF, and the solution was cooled at −78 °C. Sodium borohydride (0.02 g, 0.05 mmol) was added, and the mixture was stirred overnight, allowing the temperature to gradually rise to room temperature. Excess reagent was destroyed with 10% hydrochloric acid solution, the solvent was removed, the residue was taken up in ether, and the ethereal solution was processed as usual. Evaporation of the solvent and chromatography (EtOAc–hexanes 15:85) gave 0.034 g of **34** and 0.0085 g of its epimer (80%). For **34**: $[\alpha]^{25}_C$ +59.75° (*c* 0.4, $CHCl_3$); IR (film) 3570, 1720 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$) δ (ppm) 5.71–5.62 (m, 1 H), 5.43–5.35 (m, 1 H), 5.20–5.14 (m, 1 H), 4.27–4.18 (m, 1 H), 3.94–3.87 (m, 1 H), 2.79–2.72 (m, 1 H), 2.54–2.41 (m, 1 H), 2.23 (q, 1 H, *J* = 7.0 Hz), 2.30–2.21 (m, 1 H), 2.12–1.20 (m, 18 H), 1.13 (d, 3 H, *J* = 7.0 Hz), 1.09 (d, 3 H, *J* = 7.5 Hz), 0.91 (t, 3 H, *J* = 7.5 Hz), 0.88 (s, 9 H), 0.82 (d, 3 H, *J* = 7.0 Hz), 0.08 (s, 3 H), 0.07 (s, 3 H); MS *m/e* 165, 137, 123, 97, 81, 71.

Mitsunobu Reaction on Epimeric 34. Diethyl azodicarboxylate (0.017 mL, 0.15 mmol) and formic acid (0.04 mL, 0.15 mmol) were added to 2 mL of ether, and the mixture was cooled at 0 °C. The epimeric alcohol from above (0.0085 g, 0.0165 mmol) and PPh_3 (0.0395 g, 0.15 mmol) dissolved in 2 mL of ether were added slowly at 0 °C. The cooling bath was removed and the mixture was stirred for 45 min at room temperature. Methanol (0.5 mL) was added, the solvent was evaporated, the residue was dissolved in methanol, and $NaHCO_3$, saturated solution (10 drops), was added. The solvent was removed, ether was added, and the solution was processed in the usual manner. The product obtained was chromatographed (EtOAc–hexanes 15:85) to give **34** (0.006 g, 70%).

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-[2-[2-[1(*R*)-[[*tert*-Butyldimethylsilyl]oxy]-4(*R*)-(benzyloxy)cyclopentyl]]ethyl]-2,6-dimethyl-8-[[(*S*)-2-methyl-1-oxobutyl]oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (35). Alcohol **34** (0.04 g, 0.0785 mmol) was dissolved in 7.5 mL of dry THF, and the solution was treated with a crystal of *n*-tetrabutylammonium iodide and benzyl bromide (0.06 mL, 0.5 mmol). The solution was cooled at 0 °C and NaH (60% oil dispersion, 0.125 mmol) was added. The cooling bath was removed, and the mixture was allowed to stir for 18 h at room temperature. A few drops of deionized water were added, the solution was evaporated, the residue was dissolved in ether, and the solution was processed as usual. The residue was chromatographed, using EtOAc–hexanes (1:4), to give **35** (0.0375 g, 80%), which was used in the next step.

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-[2-[2(*R*)-[1(*R*)-Hydroxy-4-(*R*)-(benzyloxy)cyclopentyl]]ethyl]-2,6-dimethyl-8-[[(*S*)-2-methyl-1-oxobutyl]oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (36). The preceding compound (0.0375 g, 0.063 mmol) was dissolved in a mixture of HF–CH_3CN (10 mL, 1 mL of 48% aqueous HF in 9 mL of CH_3CN), and the solution was stirred for 90 min. The solvent was removed, the residue dissolved in ether, and the ethereal solution was processed in the normal way. Evaporation and chromatography (EtOAc–hexanes 15:85) gave the product **36** (0.026 g, 85%): IR (film) 3450, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39–7.28 (m, 5 H), 5.68–5.61 (m, 1 H), 5.42–5.35 (m, 1 H), 5.23–5.17 (m, 1 H), 4.47 (dd, 2 H, *J* = 12 Hz), 4.06–3.90 (m, 1 H), 3.83–3.74 (m, 1 H), 2.55–2.40 (m, 1 H), 2.39–2.29 (m, 2 H), 2.28–1.15 (m, 18 H), 1.13 (d, 3 H, *J* = 7.0 Hz), 1.09 (d, 3 H, 7.5 Hz), 0.90 (t, 3 H, *J* = 7.5 Hz), 0.82 (d, 3 H, *J* = 7.0 Hz).

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-[2-[2(*R*)-[4(*R*)-(Benzyloxy)-1-oxocyclopentyl]]ethyl]-2,6-dimethyl-8-[[(*S*)-2-methyl-1-oxobutyl]oxy]-1,2,4a,5,6,7,8,8a-octahydronaphthalene (37). A solution of oxalyl chloride (0.01 mL, 0.1 mmol) and dichloromethane (1.5 mL) placed in a flask equipped with a magnetic stirrer was cooled at −60 °C. DMSO was added (0.015 mL, 0.2 mmol) and after 10 min the alcohol **36** (0.02 g, 0.05 mmol) in 1.2 mL of dichloromethane was added. After stirring for 15 min at −60 °C, triethylamine was added (0.055 mL, 0.41 mmol) and the solution was stirred for another 15 min. Deionized water (2.5 mL) was added and the mixture was stirred at room temperature for 20 min. The aqueous phase was extracted with dichloromethane and the organic phase was processed as usual. Chromatography using EtOAc–hexanes (1:9) gave compound **37** (0.0189 g, 70%), which was used as such.

***O*-Benzyldihydromevinolin (38).** The preceding compound (0.0185 g, 0.038 mmol) was dissolved in 2 mL of dry dichloromethane and 0.05 mL at a 0.8 M solution of $BF_3{\cdot}Et_2O$ in dichloromethane was added. A 10% v/v solution of bis(trimethylsilyl) peroxide[40,41] in dichloromethane was added under argon at room temperature. After 30 min, an equal portion of $BF_3{\cdot}Et_2O$ and the peroxide (0.025 mL) was added, and the addition was repeated again after 1 h. After stirring for a total of 90 min from the beginning of the reaction, the solvent was evaporated and the residue taken up in ether and washed with 5% solution of sodium thiosulfate, saturated $NaHCO_3$ solution, and brine. The ethereal solution was processed as usual, and the residue was chromatographed, using EtOAc–hexanes 1:4, to give the title compound (0.02 g, 78%): mp 101–101.5 °C; $[\alpha]^{25}_D$ +53.33° (*c* 0.045, $CHCl_3$); IR (film) 2920, 1720, 1600, 1450, 1250, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39–7.30 (m, 5 H), 5.68–5.62 (ddd, 1 H, J_1 = 2.4 Hz, J_2 = 4.8 Hz, J_3 = 9.5 Hz), 5.40–5.37 (d, 1 H, *J* = 9.9 Hz), 5.20–5.17 (m, 1 H), 4.57–4.50 (m, 3 H), 3.99–3.96 (m, 1 H), 2.74–2.27 (m, 5 H), 2.17–1.18 (m, 14 H), 1.15–1.09 (dd, 6 H, *J* = 6.9 Hz), 0.92–0.87 (t, 3 H, *J* = 7.2 Hz), 0.85–0.83 (d, 3 *H*, *J* = 6.9 Hz); HRMS (EI) calcd for $C_{31}O_5H_{44}$–$C_5O_2H_{10}$ 394.2506, found 394.2475.

Dihydromevinolin (4). To a magnetically stirred solution of **38** (0.018 g, 0.045 mmol) in dry dichloromethane (2 mL) at −78 °C was added boron trichloride (0.23 mL, 0.23 mmol of a 1 M solution in hexanes) at −78 °C under argon, over 4 h. The reaction mixture was stirred for an additional 4 h; then it was poured into 2.5 mL of a pH 7 1 M phosphate buffer and the solution was stirred at ambient temperature for 1 h. Ethyl acetate (25 mL) and H_2O (5 mL) were added to the mixture and the organic phase was separated and washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography using EtOAc–hexanes (1:4) and then EtOAc–hexanes (3:7) gave dihydromevinolin (5 mg, 42%, 50% based the recovered material, 3 mg): mp 135–136 °C; $[\alpha]^{25}_D$ +147.40° (*c* 0.46, CH_3CN) reported,[6] mp 131–132 °C; $[\alpha]^{25}_D$ +148.6° (*c* 0.52, CH_3CN); IR (film) 2920, 1720, 1450, 1250, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.68–5.62 (ddd, 1 H, J_1 = 2.4 Hz, 5.1 Hz, J_3 = 9.7 Hz), 5.40–5.37 (d, 1 H, *J* = 9.9 Hz), 5.20–5.19 (m, 1 H), 4.64–4.57 (m, 1 H), 4.39–4.34 (m, 1 H), 2.78–2.27 (m, 5 H), 2.08–1.19 (m, 14 H), 1.15–1.08 (dd, 6 H, *J* = 6.9 Hz), 0.93–0.88 (t, 3 H, *J* = 7.2 Hz), 0.86–0.84 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) 176.11, 169.97, 132.44, 130.90, 76.050, 69.82, 62.67, 41.87, 41.74, 38.58, 38.54, 37.29, 36.08, 35.64, 32.88, 31.25, 30.81, 26.64, 23.05, 21.01, 16.36, 14.80, 11.68; HRMS (EI) calcd for $C_{24}O_5H_{38}$–$C_5O_2H_{10}$ 304.2037, found 304.2027.

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23, 129264-80-8; 24, 129264-81-9; 24 nitro alcohol derivative, 129285-44-5; 25, 116097-26-8; 26, 116180-69-9; 27, 129264-82-0; 28, 129264-83-1; 29, 129264-84-2; 30, 129264-85-3; 31, 61305-35-9; 32, 129264-86-4; 33, 129264-87-5; 34, 129264-88-6; 35, 129264-89-7; 36, 129264-90-0; 37, 129264-91-1; 38, 129264-92-2; 39, 129264-93-3; L-glutamic acid, 56-86-0; (4S)-4-[[(*tert*-butyldiphenylsilyl)oxy]-nethyl]-4-butanolide, 102717-29-3; dimethyl methylphosphonate, 756-79-6; crotonaldehyde, 4170-30-3; (phenylselenyl)acetic acid, 17893-46-8; nitromethane, 75-52-5; (S)-2-methylbutyric anhydride, 84131-91-9.

Supplementary Material Available: ^{1}H NMR spectra of all important intermediates (28 pages). Ordering information is given on any current masthead page.

Synthesis of 2,2-Dialkyl-1-aminocyclopropanecarboxylic Acids from α-Chloro Ketimines

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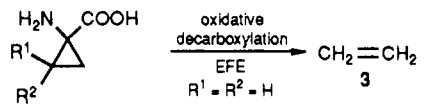
2,2-Dialkyl-1-aminocyclopropanecarboxylic acids, abbreviated as 2,2-dialkyl Acc's, are potential plant growth regulators which were synthesized by ring closure of α-chloro imines. The synthetic scheme leading to these Acc analogues entails a newly developed regiospecific synthesis of tertiary α-chloro ketimines, the trapping with cyanide of a transient Favorskii derived cyclopropylideneamine, and the hydrolytic conversion of 1-(*N*-*tert*-butylamino)-2,2-dialkylcyclopropanecarbonitriles into the title compounds.

Introduction

1-Aminocyclopropanecarboxylic acid (**1**, Acc) holds a prime position in plant physiology as it is oxidatively decarboxylated by the so-called "ethylene-forming enzyme" (EFE) to produce ethylene **3** (Scheme I).[1] Ethylene is a major plant hormone involved in regulating a number of important physiological processes including germination, ripening of fruits, abscission of fruits and leaves, and senescence. In recent years, the mechanism of the biochemical conversion of Acc to ethylene has received a great deal of attention. It started with the finding that the biosynthesis of ethylene occurs without exchange of the cyclopropane hydrogen atoms of Acc.[2] Detailed mechanistic studies by J. Baldwin and M. Pirrung have culminated in a proposal of the mechanism of the conversion of Acc to ethylene.[3-10] They suggested a stepwise enzymatic mechanism of cyclopropane ring opening in which stereochemical equilibration is faster than the subsequent bond breaking process.[6] It is proposed that this process occurs via a sequential single-electron-transfer pathway.[8,9] Also evidence has been obtained that the product of the ethylene biosynthesis from Acc, aside from carbon dioxide, is cyanide.[11,12] The physiological importance of Acc (**1**) and ethylene (**3**) has stimulated much efforts in the development of substrates that may induce an inhibition of the ethylene production, thus allowing a potential control of the ripening process. Initially, a great deal of interest was devoted to Acc analogues having a functionalized or derivatized nitrogen atom and a modified carboxylic acid functionality.[13-18] Some of these derivatives were patented for their plant growth regulating[13-15] and fungicidal properties,[16] while other Acc analogues stimulated fruit drop[17] or can be used as defoliants.[17,18] More recently, extensive efforts have been directed toward the synthesis of Acc analogues, monosubstituted at the cyclopropane ring in order to conserve the α-amino acid moiety.[19] Some

Scheme I



1: $R^1 = R^2 = H$ (Acc)
2: $R^1, R^2 \neq H$

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(1) Yang, S. F.; Hoffman, N. E. *Ann. Rev. Plant Physiol.* **1984**, *35*, 155.
(2) Adlington, R. M.; Aplin, R. T.; Baldwin, J. E.; Rawlings, B. J.; Osborne, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1086.
(3) Adlington, R. M.; Baldwin, J. E.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 290.
(4) Baldwin, J. E.; Jackson, D. A.; Adlington, R. M.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun* . **1985**, 206.
(5) Baldwin, J. E.; Adlington, R. M.; Lajoie, G. A.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1496.
(6) Baldwin, J. E.; Adlington, R. M.; Lajoie, G. A.; Lowe, C.; Baird, P. D.; Prout, K. *J. Chem. Soc., Chem. Commun.* **1988**, 775.
(7) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1983**, *48*, 5143.
(8) Pirrung, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 7207.
(9) Pirrung, M. C. *J. Org. Chem.* **1987**, *52*, 4179.
(10) Hill, R. K.; Prakash, S. R.; Wiesendanger, R.; Angst, W.; Martinoni, B.; Arigoni, D.; Liu, H.-W.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 795.
(11) Pirrung, M. C. *Bioorg. Chem.* **1985**, *13*, 219.
(12) Pirrung, M. C.; Braumann, J. I. *Plant Physiol. Biochem.* **1987**, *25*, 55.
(13) Schroeder, R.; Lürssen, K. (Bayer A.-G.) Ger. Offen. DE 3, 133, 917 (Cl. C07c101/36), 17 Mar 1983, Appl. 27 Aug 1981; *Chem. Abstr.* **1983**, *99*, 22004.
(14) Buschmann, E.; Schulz, G.; Zeeh, B.; Jung, J. (BASF A.-G.) Ger. Offen. DE 3, 128, 148 (Cl. C07c125/065), 3 Feb 1983; *Chem. Abstr.* **1983**, *98*, 178810.
(15) Amrhein, N.; Skorupka, H.; Tophof, S. (Bayer A.-G.) Ger. Offen. DE 3, 122, 240 (Cl. C07c103/46), 23 Dec 1982, Appl. 4 June 1981; *Chem. Abstr.* **1983**, *98*, 88868.
(16) Chan, D. C. K. (Chevron Research Co.), U.S. US 4,382,954 (Cl. 424-285; A01N43/08), 10 May 1983, Appl. 343,087,27 Jan 1982; *Chem. Abstr.* **1983**, *99*, 104944.
(17) Mansuri, M. M. (Shell Int. Res. Maatschappij B. V.) Brit. UK Pat. Appl. GB, 2, 127, 802 (Cl. C07c155/09), 18 Apr 1984, Appl. 82/25, 119, 3 Sep 1982; *Chem. Abstr.* **1984**, *101*, 72318.
(18) Day. J. A.; Searle, R. J. G. (Shell Int. Res. Maatschappij B. V.) Eur. Pat. Appl. EP 51, 884 (Cl. C07c119/06), 19 May 1982, GB Appl. 80/35, 442, 5 Nov 1980; *Chem. Abstr.* **1982**, *97*, 127131.

0022-3263/90/1955-5777$02.50/0