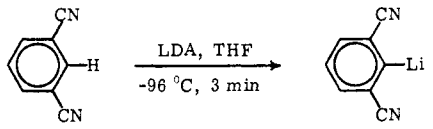
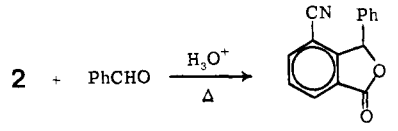


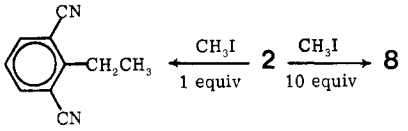
1 2

Reactions of 2 with electrophiles were carried out by a standard procedure[10] to give the expected products (Table I). Phthalide 9 was formed by heating the crude product from the reaction of 2 and benzaldehyde with dilute aqueous hydrochloric acid.

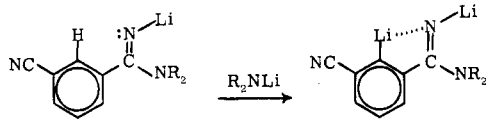


9

When 2 was treated with excess (10 equiv) methyl iodide, dicyanotoluene 8 was isolated (83%). However, when only 1 equiv of methyl iodide was added, the major product (0.33 mol/mol of 2) was 2,6-dicyano-1-ethylbenzene. We ascribe this to abstraction by 2 of the acidic benzylic proton of the initially formed 8, followed by alkylation of the benzylic anion by methyl iodide to form the ethyl compound.



Addition of an amide anion to the carbon of a nitrile function of 1 could give a species (10) whose imide nitrogen might be capable of stabilizing the lithiation product (11), and the transition state leading to it, by a chelation of lithium.[2] Since 2 equiv of the lithium amide is required to form 10, our observation that 1.05 equiv of lithium amide leads to 100% incorporation of deuterium into recovered 1 when the intermediate aryllithium species is quenched with CH_3OD rules out 11 as the structure of the aryllithium species which is deuterated. It is almost certainly 2. A base even more sterically hindered than LDA, lithium 2,2,3,6-tetramethylpiperidide, gives results similar to those seen for LDA, making nucleophilic attack at carbon seem unlikely.[11]



10 11

(9) We have recently obtained evidence for efficient ortho lithiation of 1,2-dicyanobenzene and 1,4-dicyanobenzene under the same conditions described here for 1,3-dicyanobenzene. The second cyano substitutent in the 1,2- and 1,4 isomers clearly increases the kinetic acidity of these species relative to benzonitrile.

(10) In a typical experiment, lithium diisopropylamide (LDA) [25 mL of a 0.33 M tetrahydrofuran (THF) solution, 8.2 mmol] was added dropwise over 0.5 h to a stirred solution of 1 (1.0 g, 7.8 mmol) in THF (70 mL) at −96 °C under N_2. After 0.5 h, the appropriate electrophile (usually 1.05 equiv) was added and the reaction mixture was allowed to warm slowly to room temperature. Solvent was removed under reduced pressure. The crude product was extracted from a suspension in aqueous sodium chloride with dichloromethane to remove all salts. The desired product was purified by chromatography or recrystallization from dichloromethane–pentane. Later studies indicate that if the LDA solution is cooled in a −107 °C bath and the dicyanobenzene in the minimum amount of THF is added slowly to this solution, the temperature of the solution remains below −90 °C; a highly colored, insoluble material is avoided and yields are somewhat improved.

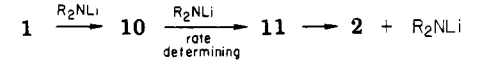
Earlier reported methods for the synthesis of 2-substituted 1,3-dicyanobenzenes include that of Mao and Boekelheide,[12] which involves the lithiation of the bis(*N,N*-dimethylhydrazone) of isophthalaldehyde. The conversion of 2-substituted isophthalic acids to the dinitriles has also been employed.[13] Another isophthalic acid equivalent, 1,3-bis(4,4-dimethyl-2-oxazolinyl)benzene, has also been successfully lithiated in the 2-position in high yield.[14] The lithiation of the relatively inexpensive dicyanobenzene provides a route to this class of compounds in fewer steps and generally with higher overall yields than the other methods.

Further work currently in progress focuses on the mechanistic implications and the synthetic potential of this reaction.

Acknowledgment. This research was supported in part by a grant from the National Cancer Institute (CA 13963). We are grateful for helpful discussions with Professors Peter Beak and Albert Meyers. Mass spectra were obtained from facilities provided under grants from the National Institutes of Health (CA 11388 and GM 16864). The University of Illinois Midwest NSF Regional NMR Facility (CHE 79-16100) provided NMR spectra.

Registry No. 1, 626-17-5; 2, 81725-15-7; 3, 81725-16-8; 4, 22433-90-5; 5, 28442-78-6; 6, 81725-17-9; 7, 81740-10-5; 8, 2317-22-8; 9, 81725-18-0; benzaldehyde, 100-52-7; 2,6-dicyano-1-ethylbenzene, 41052-95-3.

(11) We rule out a mechanism in which 10 and 11 are transient intermediates, with rate-determining lithiation of 10 to form 11 followed by rapid elimination of LDA to form 2, by the observed first-order dependence of the rate of lithiation on LDA concentration:



Pseudo-first-order rate constants for reactions carried out with a large excess of LDA are linearly related to LDA concentration over the range 0.0026–0.0104 M. A second-order rate constant (first order in both 1 and LDA) was calculated, $k_2 = 0.41\ M^{-1}\ s^{-1}$ at −98 °C. The reaction of Scheme II, which would show a second-order dependence on LDA concentration, is therefore ruled out.

(12) Mao, Y. L.; Boekelheide, V. *J. Org. Chem.* **1980**, *45*, 2746 used the directed ortho lithiation of the bis(*N,N*-dimethylhydrazone) of isophthaldehyde to prepare 2-substituted 1,3-dicyanobenzenes. While 2 could conceivably have served as an intermediate in these reactions via rapid elimination of dimethylamide anion, the reactions appear to have been carried out at room temperature and we find that 2 is unstable even at temperatures as low as −78 °C. It is therefore unlikely that 2 is in fact an intermediate in the reactions of Mao and Boekelheide.

(13) Wallenfels, K.; Witzler, F.; Friedrich, K. *Tetrahedron* **1967**, *23*, 1353.

(14) Harris, T. D.; Neuschwander, B.; Boekelheide, V. *J. Org. Chem.* **1978**, *43*, 727.

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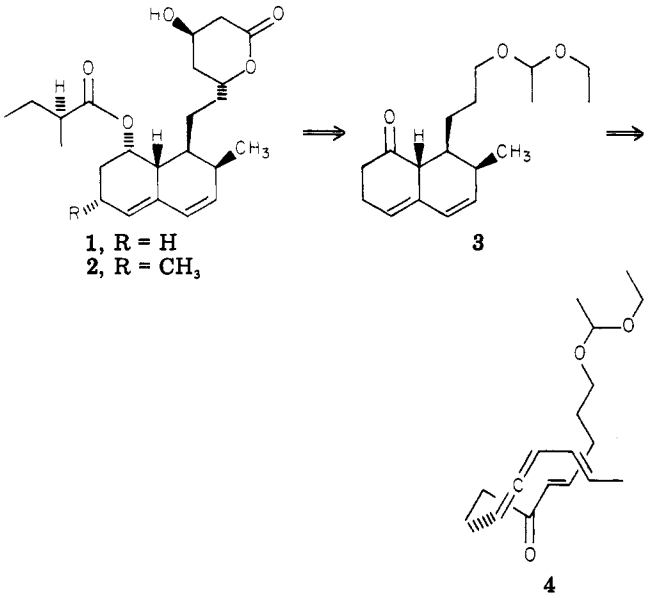
Synthesis of the Hexahydronaphthalene Moiety of (±)-Compactin (ML-236B)

Summary: An efficient synthesis of the hexahydronaphthalene moiety of compactin using an intramolecular Diels–Alder reaction with a vinylallene as the diene is described.

Sir: Compactin (1)[1] and ML-236B[2] are identical fungal

Scheme I

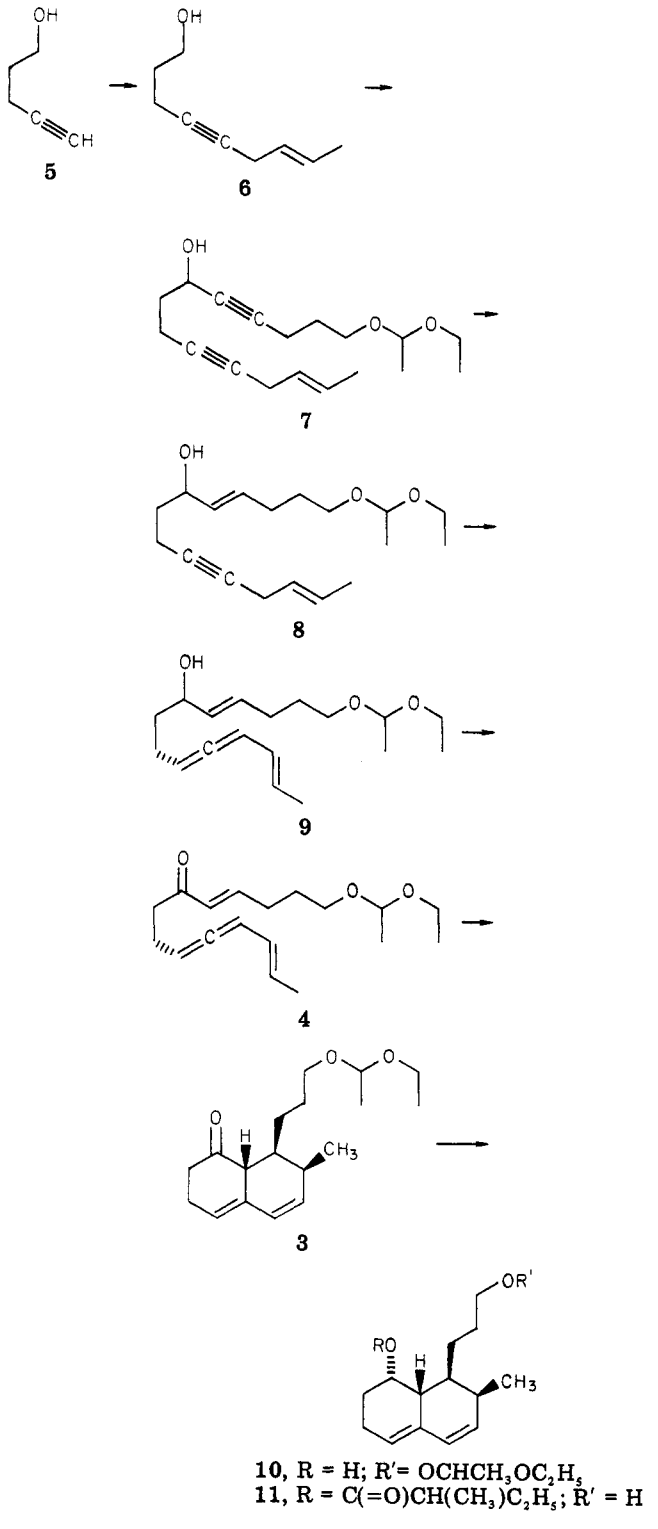


1, R = H
2, R = CH_3

3

4

Scheme II



5

6

7

8

9

4

3

10, R = H; R'= $OCHCH_3OC_2H_5$
11, R = $C(=O)CH(CH_3)C_2H_5$; R' = H

metabolites isolated from strains of *Penicillium brevicompactum* and *Penicillium citrinum*, respectively. Both compactin (1)[3] and mevinolin (2)[4] are potent competitive inhibitors of (3-hydroxy-3-methylglutaryl)coenzyme A (HMG-CoA) reductase, the enzyme which catalyzes the rate-limiting step of cholesterol biosynthesis. The observation that compactin substantially reduces serum cholesterol levels in dogs, monkeys, and humans[3] and may therefore be an effective therapeutic agent for hypercholesterolemia has prompted extensive synthetic work which has resulted in one total synthesis of (+)-compactin[5] and syntheses of the hexahydronaphthalene moiety[6] and lactone moiety[6c,7] as well as simpler analogues.[8] We report here an efficient total synthesis of the hexhydronaphthalene moiety of compactin which leads to **10** in eight steps from 4-pentyn-1-ol.

The key to our retrosynthetic analysis (Scheme I) is the intramolecular Diels–Alder reaction of **4**, in which a vinylallene is the diene component, to give **3** which contains three of the four chiral centers and the diene unit. Examination of models suggests that steric constraints would lead to the formation of the exo adduct **3** due to the rigidity of the allene. The use of vinylallenes as dienes in Diels–Alder reactions is well-known.[9] On the other hand, intramolecular Diels–Alder reactions of vinylallenes are virtually unknown,[10,11] and stereochemical information is not available.

The synthesis of **4** was efficiently accomplished as outlined in Scheme II. Conversion of 4-pentyn-1-ol (**5**)

(1) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(2) (a) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (b) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.
(3) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. *N. Engl. J. Med.* **1981**, *305*, 478 and references cited therein.
(4) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, *J. Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957 and references cited therein.
(5) Wang, N.-Y.; Hsu, C.-T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538.
(6) (a) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (b) Professor S. Danishefsky, Yale University, New Haven, CT, private communication. (c) Heathcock, C. H.; Taschner, M. J.; Thomas, J. A., "Abstracts of Papers", 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1982; American Chemical Society: Washington, DC; ORGN 13.
(7) (a) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, *23*, 281. (b) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.
(8) Sato, A.; Ogiso, A.; Noguchi, H.; Mitsui, S.; Kaneko, I.; Shimada, Y. *Chem. Pharm. Bull.* **1980**, *28*, 1509.
(9) Egenburg, I. Z. *Russ. Chem. Rev.* **1978**, *47*, 470 and references cited therein.
(10) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1974**, 496.
(11) An intramolecular Diels–Alder reaction of a substrate similar to **4** with the exception that a 3-allenylfuran is the diene has been reported to give a 10:1 mixture of unidentified stereoisomers. Reich, H. J. "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, Aug 1981; American Chemical Society: Washington, DC; ORGN 22.

to the dianion with MeMgCl in THF, addition of 6 mol % curprous chloride and coupling with 2 equiv of crotyl bromide[12] (45 min, 70 °C) gave a 10:1 mixture of **6** and the undesired product of S_N2' alkylation in 80% yield. Oxidation of this mixture with oxalyl chloride, triethylamine, and dimethyl sulfoxide[13] gave a mixture of aldehydes which was reacted with the acetylide derived from MeMgCl and the ethoxyethyl ether of 4-pentyn-1-ol to give, after chromatography, **7** (60% from **5**). Reduction of **7** with 2:1 NaOMe–$LiAlH_4$[14] (THF, 70 °C, 1.5 h) gave **8** (90%).

Base-catalyzed isomerization[9] of **8** (0.2 M **8**, 1 M KO-*t*-Bu, *t*-BuOH, 12 h, 40 °C) gave a mixture which contained ≈50% of enallene **9** along with conjugated enynes and unreacted **8**.[15] This mixture was carried through to **10** which could easily be purified chromatographically. Oxidation of **9** with PCC–NaOAc[16] (CH_2Cl_2, 25 h) gave the required tetraene **4** (80%).

Intramolecular Diels–Alder reaction to give **3** was effected by heating **4**, containing 0.5% BHT, in benzene for 2 h at 150 °C in a sealed tube. Due to the anticipated instability of β,γ-unsaturated ketone **3**,[17] the crude mixture was immediately reduced with L-Selectride (THF, 0 °C, 30 min) to give **10** (30% from **8**, ≈75% from **4**).[18]

The structure of **10** was proven by conversion to **11** (as a mixture of diastereomers, one of which is an intermediate in Wang, Hsu, and Sih's synthesis of (+)-compactin).[5] Esterification of **10** with (*S*)-2-methylbutyric anhydride[5] and deprotection (HOAc/THF/H_2O, 3:2:1)[5] gave **11**, mp 54.5–55.5 °C, as a mixture of diastereomers. The NMR and IR spectra and HPLC retention times of this mixture were identical with those of the natural stereoisomer kindly provided by Professor Sih.[19]

Funk and Zeller have previously synthesized the hexahydronaphthalene moiety of compactin by an intramolecular Diels–Alder reaction.[6a] Their cycloaddition leads to an octahydronaphthalene which must be brominated and dehydrobrominated to give the desired product.

The intramolecular Diels–Alder reaction using a vinylallene as the diene has several advantages as a synthetic method. The vinylallene can be synthesized by isomerization of a readily available 1,4-enyne, the allene can be synthesized in optically active form, providing a simple means for the asymmetric synthesis of Diels–Alder adducts, and highly functionalized adducts are obtained. Studies directed toward determining the scope of this reaction and its application to the synthesis of chiral hexahydronaphthalene moieties of compactin and mevinolin are presently underway.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (GM-30528). The 270-MHz NMR spectrometer was purchased with funds provided by the National Institutes of Health (BM 20168). We thank Professor Sih for a comparison sample of his synthetic intermediate.

Registry No. **3**, 81790-71-8; **4**, 81790-72-9; **5**, 5390-04-5; **6**, 81790-73-0; **7**, 81790-74-1; **8**, 81790-75-2; **9**, 81790-76-3; **10**, 81790-77-4; **11** (isomer 1), 81844-72-6; **11** (isomer 2), 81844-73-7; crotyl bromide, 4784-77-4.

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(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(14) Molloy, B. B.; Hauser, K. L. *Chem. Commun.* **1968**, 1017.
(15) An alternate route, in which **6** was isomerized to the enallene prior to oxidation to the aldehyde and coupling with acetylide, failed since the triple bond of the propargylic alcohol could not be reduced in the presence of the vinylallene.
(16) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(17) McGahren, W. J.; Ellestad, G. A.; Morton, G. O.; Kunstmann, M. P. *J. Org. Chem.* **1976**, *41*, 66.
(18) Although the analysis of this mixture was complicated by the presence of byproducts from the isomerization of **8**, no isomeric Diels–Alder adducts could be detected.
(19) The 270-MHz NMR spectra of our mixture showed two doublets, separated by 0.004 ppm, for the 2-methyl group of the ester. The downfield peak corresponds to that of Sih's sample. Under some analytical HPLC conditions partial separation of our mixture could be obtained (Waters RCM-100, 10-μm silica gel radial-Pak cartridge, 9:1 hexane–$CHCl_3$, 5 mL/min; t_R = 40 and 43 min). The slower moving isomer corresponds to Sih's sample.

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