Studies Directed Toward the Synthesis of Taxanes: Construction of the Tricyclo[5.3.1.0^{1,7}]undecane System

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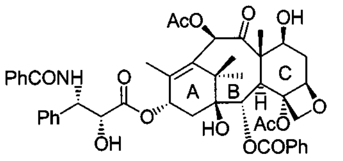
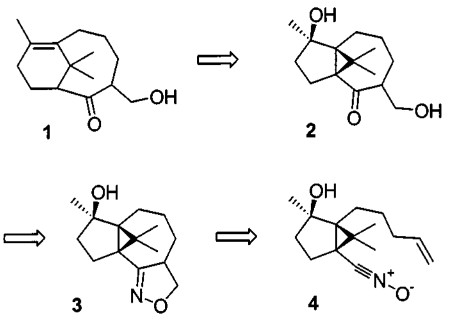
The intramolecular nucleophilic substitution of an epoxide by the anion of a nitrile was used to construct the bicyclo[3.1.0]hexane system of **9**, derived from **8**, and of **14**, derived from **13**. The intramolecular 1,3-dipolar cycloaddition of nitrile oxide **4**, obtained from **14**, led to isoxazoline **3**. However, it was not possible to convert **3** into the corresponding β-hydroxy ketone. Rearrangements of **3** were observed in the presence of dehydrating reagents leading to compounds **19–21**, which are structurally related to 11(15→1)abeotaxanes.

Various strategies have been employed to prepare taxol and other taxane compounds. Convergent approaches based on the formation of the B ring from a compound which already has the A and C rings are handicapped by the difficulty of cyclizing this eight-membered ring.[1] The fragmentation of small rings to construct the A/B system may be seen as an alternative. Several fragmentations of cyclopropanes included in bicyclic or tricyclic systems have been reported.[2]

Our own strategy to gain access to the taxane A/B system is summarized in Scheme 1. The bicyclic compound **1** could be derived from compound **2** by a process involving the regioselective breaking of a carbon-carbon bond of the cyclopropane ring included in the tricyclo[5.3.1.0^{1,7}]undecane system, and the subsequent elimination of the tertiary hydroxyl group to establish the double bond of the A ring. The isoxazoline **3**, which should serve as a precursor to the β-hydroxy ketone **2**, would itself arise from the intramolecular 1,3-dipolar cycloaddition of nitrile oxide **4**; it was expected that the formation of a seven-membered ring by this method would be much easier than the formation of an eight-membered ring.

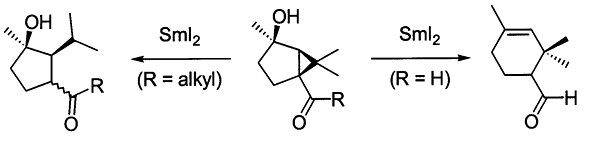


taxol



Scheme 1. Retrosynthetic analysis

With respect to the fragmentation of the cyclopropane ring and the subsequent elimination of water that would lead to product **1** from the tricyclic compound **2**, we recently reported a study in which samarium(II) iodide was used to induce such a transformation.[3] It must be pointed out that when bicyclo[3.1.0]hexanes were employed as substrates, the regioselectivity of the cyclopropane opening was dependent on the nature of the carbonyl group present in the molecule, aldehydes leading to cyclohexenes and ketones leading to cyclopentanols (Scheme 2). However, the result of the fragmentation of a tricyclic ketone such as **2** cannot be easily anticipated as it should depend on the conformation of the compound in solution.



Scheme 2. SmI$_2$-mediated fragmentation of bicyclo[3.1.0]hexanes

In this article, we present the synthesis of isoxazoline **3** and the results of the fragmentation of the cyclopropane ring of this compound. A short reaction sequence that allowed the formation of a model bicyclo[3.1.0]hexane system was designed in the first place. It was based on the intramolecular formation of the cyclopropane ring by the nucleophilic substitution of an epoxide by a nitrile anion, as depicted in Scheme 3. Thus, a Diels−Alder reaction of 2,4-dimethyl-1,3-pentadiene (**5**) with 2-chloroacrylonitrile (**6**) afforded cyclohexene **7**.[4] Epoxide **8** was then obtained, as a mixture of diastereomers, by treatment of **7** with *m*-CPBA. Dechlorination of **8** with phenyllithium produced

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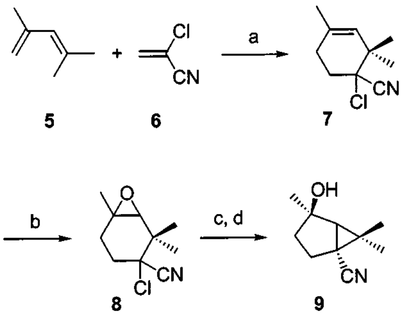
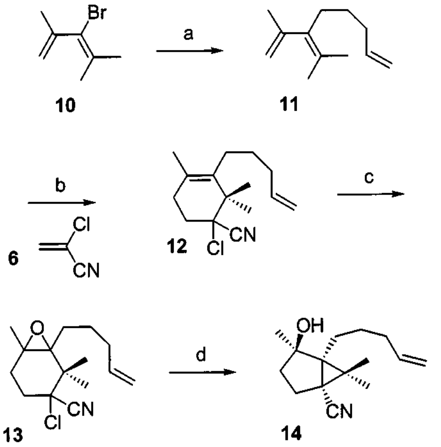
the corresponding nitrile which was then treated with lithium diisopropylamide to give the bicyclic compound **9** as a single diastereomer. It was also possible to convert **8** to **9** in a one-pot procedure: after treatment of **8** with phenyllithium for 30 min, diisopropylamine (2 equiv.) was added and the reaction stirred at room temperature for 13 h. In this case **9** was isolated in a slightly lower yield (66%).



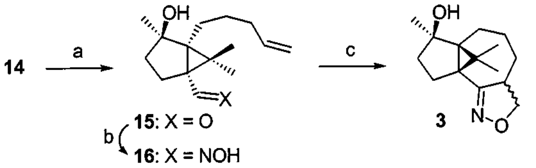
Scheme 3. Preparation of nitrile **9**; reagents and conditions: (a) ref.[4]; (b) *m*-CPBA, CH_2Cl_2, 0°C, 26 h, 97%; (c) PhLi (2 equiv.), THF, −78°C, 30 min, 86%; (d) *i*Pr_2NLi, THF, −78°C to room temp., 13 h, 94%

The same sequence was then applied to the synthesis of the nitrile **14**, which contains a 4-pentenyl chain (Scheme 4). Treatment of the alkenyllithium reagent derived from 3-bromo-2,4-dimethylpenta-1,3-diene (**10**)[5] with 5-bromopent-1-ene afforded the triene **11**, which was converted into diene **12** by a Diels−Alder reaction with 2-chloroacrylonitrile at 120°C for 15 days. Epoxidation of diene **12** was then performed by treatment with *m*-CPBA in CH_2Cl_2 at 0°C. A mixture of recovered **12** (32%), epoxide **13** (50%, two diastereomers) and the product of epoxidation at the terminal olefin (17%) was obtained when one equivalent of reagent was used. Adding more *m*-CPBA did not improve the yield of **13**, but instead led to the formation of undesired bis(epoxides). A one-pot conversion of epoxide **13** to the bicyclic nitrile **14** proceeded smoothly under the same experimental conditions as for the synthesis of **9**.



Scheme 4. Preparation of nitrile **14**; reagents and conditions: (a) *t*BuLi, THF, −78°C, 1 h, then 5-bromopent-1-ene, −78°C to room temp., 15 h, 90%; (b) **6**, 120°C, 15 days, 69%; (c) *m*CPBA, CH_2Cl_2, 0°C, 13 h, 50%; (d) PhLi (2 equiv.), THF, −78°C, 20 min, then *i*Pr_2NH (2 equiv.), −78°C to room temp., 12 h, 71%.

The synthesis of isoxazoline **3** from nitrile **14** was then carried out as described in Scheme 5. Reduction of the nitrile function and conversion of the obtained aldehyde **15** to the corresponding oxime **16** both proceeded in excellent yields. Refluxing a highly diluted chloroform solution of **16** in the presence of excess NaOCl in water gave the tetracyclic isoxazoline **3** as a 93:7 mixture of epimers in 81% yield. The relative configuration of the major epimer could not be determined by nOe experiments. We were unable to obtain crystals suitable for an X-ray diffraction analysis. The result of the cycloaddition constrasted sharply with our previous, unfruitful attempts to construct directly the eight-membered A ring of the bicyclic A/B system of taxanes.[1]

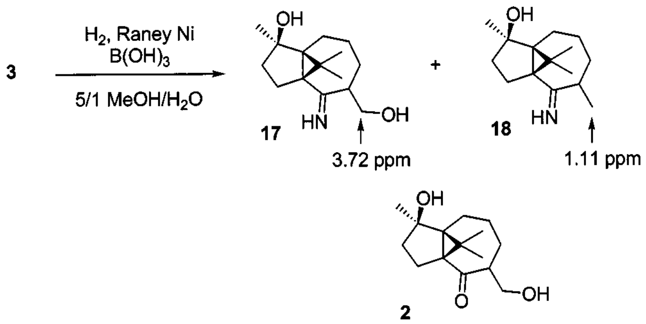


Scheme 5. Preparation of isoxazoline **3**; reagents and conditions: (a) *i*Bu_2AlH, Et_2O, 0°C, 2 h; (b) $H_2NOH.HCl$, Na_2CO_3, CH_2Cl_2/H_2O, 99%; (c) 7% aq. NaOCl, $CHCl_3$ ($c = 10^{-3}$ M), reflux, 36 h, 81%.

The next planned step was the cleavage of the isoxazoline ring to generate the corresponding β-hydroxy ketone **2**, which would then be treated with reagents that can fragment the cyclopropane ring. Hydrogenolysis according to the method developped by Curran (H_2, Raney Ni, $B(OH)_3$, 5:1 $MeOH/H_2O$),[6] however, did not yield the expected ketone **2**. The signals corresponding to the protons on the isoxazoline ring were no longer present in the ^1H NMR spectrum of the crude product, but no evidence of a carbonyl stretch was found in the IR spectrum (Scheme 6). Instead, a band at 1621 cm^{-1} indicated the presence of an imine function. According to the ^1H NMR spectrum, the crude product consisted of a mixture of imines **17**, characterized by a doublet at $\delta = 3.72$ ($J = 6.8$ Hz, 2 H) and **18**, characterized by a doublet at $\delta = 1.11$ ($J = 6.8$ Hz, 3 H). Compound **18** apparently arose from the β-elimination of the primary alcohol of **17**, followed by the hydrogenation of the formed α,β-unsaturated imine. Ketone **2** was not produced, even after prolonged reaction times. The resistance of the imine function toward hydrolysis could be attributed to steric congestion. Other authors have reported the isolation of stable β-hydroxy imines as cleavage products of isoxazolines, and the conditions allowing their conversion into the corresponding β-hydroxy ketones.[7] However, in our case, treatment of the crude mixture of imines **17** and **18** under similar conditions led only to degradation products. This was probably due to a facile elimination of the tertiary hydroxyl group, followed by rearrangements.

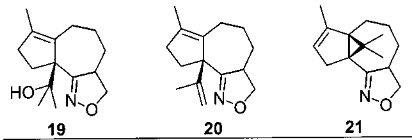
Cleaner rearrangements were observed from **3** in the presence of several dehydrating reagents; varying amounts of isoxazolines **19**−**21** were obtained (Table 1).

While **21** is the product of a simple dehydration of **3**, the formation of both compounds **19** and **20** involves the fragmentation of the cyclopropane ring, probably via the



Scheme 6. Hydrogenolysis of isoxazoline **3**

Table 1. Cleavage of the cyclopropane ring of isoxazoline **3**

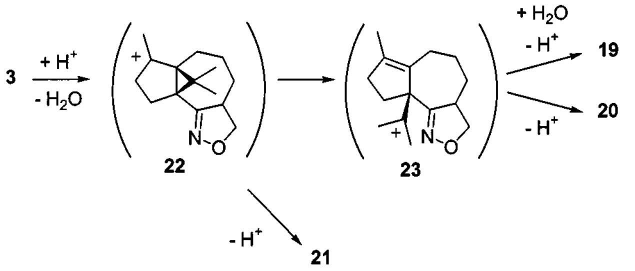


19 **20** **21**

Reagent	Solvent	Temperature, time	Product
Burgess reagent (2 equiv.)	benzene	room temp., 27 h then reflux, 3 h	**20** + **21** (90:10, 54%)
Amberlyst-15	1:1 THF/H_2O	room temp., 3 days	**19** (72%)
Amberlyst-15	toluene + ε H_2O	room temp., 27 h	**19** (38%) **20** + **21** (75:25, 42%)
MsCl (6.4 equiv.), Et_3N	CH_2Cl_2	room temp., 2 days	**20** + **21** (80:20)[a]

[a] The product of this reaction was not further purified.

cationic intermediates **22** and **23** (Scheme 7), which, depending on the nature of the solvent, can lose a proton to yield alkene **20** or react with water, affording alcohol **19**. These two compounds are structurally related to 11(15→1)abeotaxanes, such as brevifoliol (**24**)[8] and taxchinin A (**25**) (Figure 1).[9]



Scheme 7. Formation of compounds **19**, **20**, **21** from isoxazoline **3**

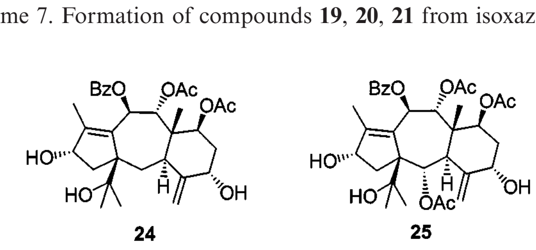


Figure 1. Molecular structures of **24** and **25**

The treatment of compound **3** with other reagents known to cleave isoxazoline rings, such as ozone[10] or molybdenum hexacarbonyl[11] was not successful. Reaction with samarium(II) iodide in THF left compound **3** unchanged, although a decoloration of the solution from blue to yellow was observed.

In conclusion, a new route to compounds with the bicyclo[3.1.0]hexane system, based on the formation of the cyclopropane ring by an intramolecular nucleophilic substitution of an epoxide by a nitrile anion, was designed. The construction of a fused seven-membered ring from a 1,3-dipolar cycloaddition leading to isoxazoline **3** was, as expected, much easier than the direct cyclization of the eight-membered ring of the taxane A/B bicyclic system. However, we could not find suitable reaction conditions for the generation of the β-hydroxy ketone **2**, partly because of the stability of the sterically crowded imine function toward hydrolysis. Thus another method should be used to cyclize the seven-membered ring. Dehydration of isoxazoline **3** gave rise to compounds that are structurally related to 11(15→1)abeotaxanes.

Experimental Section

General: All reactions were performed under an atmosphere of argon. − THF was freshly distilled from sodium benzophenone ketyl. − TLC: Silica Gel 60F_{254} plates (Merck), with detection by UV light or with a solution of phosphomolybdic acid in EtOH. − Column chromatography: 40−63 μm Merck Silica Gel. − IR: Perkin−Elmer 2000. − Melting points (uncorrected): Büchi 535. − NMR: Bruker AM 300 (300.13 and 75.47 MHz for ^1H and ^{13}C, respectively). − MS: Finnegan-Mat 4600 (70 eV).

3-Chloro-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptane-3-carbonitrile (8): *m*-Chloroperbenzoic acid (3.39 g, 19.7 mmol) was added portionwise to a solution of alkene **7** (3.0 g, 16.4 mmol) in dichloromethane (109 mL) cooled to 0°C. The reaction was allowed to warm to room temperature. After stirring for 14 h, the reaction was incomplete. A further portion of *m*-chloroperbenzoic acid (850 mg) was added at this time, and then again after 2 h (1 g). Stirring was continued for 10 h. The reaction mixture was then concentrated in vacuo. Chromatography on silica gel (hexane/AcOEt, 9:1) afforded 3.26 g (97%) of epoxide **8** as a 55:45 mixture of diastereomers; samples of each one were separated. − Less polar diastereomer (minor): IR (film): $\tilde{\nu}$ = 2998, 2935, 2878, 2240, 1471, 1458, 1425, 1384, 1370, 1322, 1234, 1085, 1038, 1020, 1002, 948, 939, 894, 874, 814, 778, 590 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 2.70 (s, 1 H), 1.88−2.22 (m, 4 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.18 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 117.7, 65.4, 64.4, 58.9, 38.2, 30.8, 28.8, 24.8, 22.3, 19.8. − More polar diastereomer (major): IR (film): $\tilde{\nu}$ = 2977, 2931, 2876, 1469, 1449, 1389, 1217, 1090, 1018, 984, 937, 916, 895, 834, 819 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 2.63 (s, 1 H), 1.95−2.21 (m, 4 H), 1.34 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 118.0, 64.4, 64.2, 58.0, 38.3, 30.0, 25.6, 25.0, 22.9, 22.6.

2,2,6-Trimethyl-7-oxabicyclo[4.1.0]heptane-3-carbonitrile: A solution of phenyllithium (94 mL, 1.6 M in cyclohexane/ether 70:30, 15.1 mmol) was added dropwise to a solution of epoxide **8** (1.5 g, 7.54 mmol) in THF (75 mL) cooled to −78°C. After stirring for 30 min at this temperature, saturated aqueous ammonium chloride (10 mL) was added. The organic layer was separated, the aqueous phase extracted with ether (3 × 100 mL) and then the combined organic phases were dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/ether, 7:3) afforded 1.13 g (86%) of the title compound as a 51:49 mixture of diasteromers; samples of each one were separated. − Less polar diastereomer: − IR (film): $\tilde{\nu}$ = 2966, 2936, 2876, 2238, 1466, 1389, 1381, 1370, 1030, 927, 888, 794 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 2.64 (s, 1 H), 2.49 (dd, *J* = 3.9, 10.2 Hz, 1 H), 1.59−1.90 (m, 4 H), 1.29 (s, 3 H), 1.19 (s, 3 H), 1.18 (s, 3 H) − ^{13}C NMR (CDCl$_3$): δ = 120.6, 69.9, 58.4, 33.5, 32.8, 26.3, 25.4, 23.8, 21.2, 20.7. − MS (CI, NH$_3$); *m/z* (%):183 (100) [M$^+$ + NH$_4$]. − More polar diastereomer: − IR (film): ṽ = 2966, 2931, 2875, 2238, 1469, 1452, 1428, 1389, 1380, 1370, 1092, 1023, 918, 890, 814, 734 cm^{-1}. − ^{1}H NMR (CDCl$_3$): δ = 2.61 (s, 1 H), 2.13 (dd, *J* = 3, 11.1 Hz, 1 H), 1.97−2.04 (m, 1 H), 1.60−1.75 (m, 3 H), 1.31 (s, 3 H), 1.20 (s, 3 H), 1.19 (s, 3 H) − ^{13}C NMR (CDCl$_3$): δ = 120.1, 65.9, 58.6, 37.3, 31.6, 29.4, 27.6, 22.7, 20.83, 20.77. − MS (CI, NH$_3$); *m/z* (%):183 (100) [M$^+$ + NH$_4$].

4-Hydroxy-4,4,6-trimethylbicyclo[3.1.0]hexane-1-carbonitrile (9): Butyllithium (4.1 mL, 6.55 mmol, 1.6 M in hexanes) was added to a solution of diisopropylamine (919 mL, 6.55 mmol) in THF (10 mL) cooled to 0°C. After stirring for 20 min at this temperature, the solution of lithium diisopropylamide was cooled to −78°C and was then added via a cannula to a solution of 2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptane-3-carbonitrile (541 mg, 3.28 mmol) in THF (10 mL), at −78°C. The reaction mixture was allowed to warm to room temperature and stirred for 13 h. Saturated aqueous ammonium chloride (10 mL) was then added. The organic layer was separated and the aqueous phase extracted with ether (3 × 20 mL). The combined organic phases were washed to neutrality with saturated aqueous ammonium chloride, then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/AcOEt, 8:2), afforded 509 mg (94%) of nitrile **9**. − ^{1}H NMR (CDCl$_3$): δ = 2.22 (dt, *J* = 14.1, 9.9 Hz, 1 H), 2.10 (ddd, *J* = 14.1, 9.9, 2.1 Hz, 1 H), 1.90 (ddd, *J* = 14.1, 9.9, 2.1 Hz, 1 H), 1.70 (dt, *J* = 14.1, 9.9 Hz, 1 H), 1.68 (s, 1 H), 1.48 (s, 3 H), 1.37 (s, 3 H), 1.27 (s, 3 H). − ^{13}C NMR (CDCl$_3$): δ = 121.7, 79.7, 48.6, 39.5, 31.3, 29.4, 27.2, 26.8, 26.7, 15.7.

Triene 11: To a solution of vinyl bromide **10** (10.3 g, 58.7 mmol) in THF (125 mL) cooled to −78°C was added dropwise a solution of *tert*-butyllithium (725 mL, 1.7 M in pentane, 123 mmol). After stirring for 1 h at this temperature, 5-bromopent-1-ene (8.34 mL, 70.5 mmol) was added dropwise. The reaction mixture was stirred for 2 h at −78°C, then allowed to warm to room temperature and stirred for 15 h. Water (100 mL) was then added. The organic layer was separated and the aqueous phase extracted with pentane (3 × 100 mL). The combined organic phases were washed to neutrality with saturated aqueous ammonium chloride, then with brine (100 mL), and dried over magnesium sulfate. After filtration and concentration in vacuo, 8.6 g (90%) of nitrile **9** was obtained as an oil; it was used in the next step without further purification. − IR (film): ṽ = 3076, 2977, 2927, 2859, 1641, 1442, 1371, 1189, 1123, 1071, 1037, 991, 910, 894 cm^{-1}. − ^{1}H NMR (CDCl$_3$): δ = 5.81 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H), 4.9−5.0 (m, 3 H), 4.53 (d, *J* = 2.1 Hz, 1 H), 2.08 (t, *J* = 7.5 Hz, 2 H), 2.04 (dt, *J* = 6.6, 7.5 Hz, 2 H), 1.74 (s, 3 H), 1.66 (s, 6 H), 1.42 (tt, *J* = 7.5, 7.5 Hz, 2 H). − ^{13}C NMR (CDCl$_3$): δ = 146.4, 138.8, 136.3, 124.7, 114.0, 112.7, 33.4, 30.3, 27.4, 22.4, 21.4, 19.4.

1-Chloro-3-(pent-4-enyl)-2,2,4-trimethylcyclohex-3-ene-1-carbonitrile (12): 2-Chloroacrylonitrile (2.77 mL, 34.8 mmol) and triene **11** (3.8 g, 23.2 mmol) were charged in a thick-walled tube. After heating for 5 days at 120°C, triene was still present in the reaction mixture; a further amount of 2-chloroacrylonitrile (0.44 mL, 5.5 mmol) was added and heating was continued for 5 days. The reaction mixture was then cooled to room temperature, the solution transferred to a flask and the tarry residue was washed with dichloromethane. The combined organic phases were concentrated in vacuo. Chromatography on silica gel (pentane/ether, 99:1) afforded 4.0 g (69%) of nitrile **12**. − IR (film): ṽ = 3077, 2979, 2944, 2908, 2865, 2842, 2241, 1824, 1641, 1475, 1459, 1436, 1390, 1369, 1323, 993, 913, 871, 735 cm^{-1}. − ^{1}H NMR (CDCl$_3$): δ = 5.79 (ddt, *J* = 16.8, 9.9, 6.9 Hz, 1 H), 5.01 (d, *J* = 16.8 Hz, 1 H), 4.97 (d, *J* = 9.9 Hz, 1 H), 2.1−2.35 (m, 4 H), 2.06 (dt, *J* = 7.5, 6.9 Hz, 2 H), 1.99 (dt, *J* = 8.1, 17.1 Hz, 2 H), 1.62 (s, 3 H), 1.46 (tt, *J* = 7.5, 8.1 Hz, 2 H), 1.36 (s, 3 H), 1.22 (s, 3 H). − ^{13}C NMR (CDCl$_3$): δ = 138.0, 133.7, 126.1, 118.9, 114.7, 67.3, 43.4, 34.0, 32.6, 29.4, 28.7, 28.6, 24.4, 23.4, 19.3. − MS (CI, NH$_3$); *m/z* (%): 269 (100) [M$^+$ + NH$_4$].

Epoxide 13: *m*-Chloroperbenzoic acid (80%, 808 mg, 4 mmol) was added to a solution of alkene **12** (997 mg, 4 mmol) in dichloromethane (40 mL) cooled to 0°C. The reaction was allowed to warm to room temperature with vigorous stirring. After 13 h, water (10 mL) was added The organic layer was then separated and the aqueous phase extracted with ether (3 × 20 mL). The combined organic phases were washed successively with saturated aqueous NaHCO$_3$ (10 mL) and brine (10 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, the residue obtained was chromatographed on silica gel (hexane containing increasing amounts of ether: from 0.5% to 15%). Unreacted alkene **12** (330 mg, 32%), the two diastereomers of epoxide **13** (less polar isomer: 240 mg, 23%; more polar isomer: 250 mg, 27%) and the product of epoxidation at the monosubstituted double bond (178 mg, 17%) were successively eluted. − Less polar diastereomer: ^{1}H NMR (CDCl$_3$): δ = 5.75 (ddt, *J* = 6.9, 10.2, 17.1 Hz, m, 1 H), 5.01 (d, *J* = 17.1 Hz, 1 H), 4.96 (d, *J* = 10.2 Hz, 1 H), 1.5−2.3 (m, 10 H), 1.18 (s, 3 H), 1.35 (s, 3 H), 1.49 (s, 3 H). − ^{13}C NMR (CDCl$_3$): δ = 137.5, 118.1, 115.2, 68.1, 63.6, 66.2, 42.7, 34.0, 31.7, 30.8, 30.7, 25.6, 25.1, 20.3, 19.8. − MS (CI, NH$_3$); *m/z* (%): 268 (20) [M$^+$ + H], 285 (100) [M$^+$ + NH$_4$]. − C$_{15}$H$_{22}$ClNO (267.8): calcd. C 67.28, H 8.28, N 5.23; found C 67.27, H 8.45, N 5.01. − More polar diastereomer: IR (film): ṽ = 3077, 2960, 2929, 2241, 1641, 1477, 1456, 1444, 1394, 1373, 1120, 1022, 993, 914, 854 cm^{-1}. − ^{1}H NMR (CDCl$_3$): δ = 5.74 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1 H), 4.99 (d, *J* = 17.1 Hz, 1 H), 4.95 (d, *J* = 10.2 Hz, 1 H), 1.9−2.3 (m, 6 H), 1.5−1.7 (m, 4 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.29 (s, 3 H). − ^{13}C NMR (CDCl$_3$): δ = 137.6, 118.6, 115.1, 67.1, 62.5, 66.7, 42.5, 33.9, 30.2, 30.0, 27.8, 25.1, 23.0, 22.6, 20.4. − MS (CI, NH$_3$); *m/z* (%): 268 (10) [M$^+$ + H], 285 (100) [M$^+$ + NH$_4$]. − C$_{15}$H$_{22}$ClNO (267.8): calcd. C 67.28, H 8.28, N 5.23; found C 67.18, H 8.49, N 5.06.

Product of epoxidation at the monosubstituted double bond: ^{1}H NMR (CDCl$_3$): δ = 2.91 (m, 1 H), 2.74 (t, *J* = 4.8 Hz, 1 H), 2.45 (dd, *J* = 4.8, 2.7 Hz, 1 H), 2.40−2.15 (m, 4 H), 2.10−2.00 (m, 2 H), 1.62 (s, 3 H), 1.60−1.40 (m, 4 H), 1.36 (s, 3 H), 1.25 (s, 3 H). − ^{13}C NMR (CDCl$_3$): δ = 133.4, 133.3, 126.4, 118.5, 118.2, 67.2, 51.8, 46.7, 43.3, 32.6, 29.4, 29.1, 26.1, 24.3, 23.4, 19.3. − MS (CI, NH$_3$); *m/z* (%): 285 (100) [M$^+$ + NH$_4$]. − C$_{15}$H$_{22}$NO [M$^+$ − Cl]: calcd. 232.1701; found 232.1733 (HRMS).

Nitrile 14: A solution of phenyllithium (2.4 mL, 1.6 M in 7:3 cyclohexane/ether, 3.84 mmol) was added dropwise to a solution of epoxide **13** (550 mg, 1.92 mmol) in THF (20 mL) cooled to −78°C. After stirring at this temperature for 20 min, diisopropylamine (0.54 mL, 3.84 mmol) was added and the reaction allowed to warm to room temperature. After stirring for 12 h, saturated aqueous ammonium chloride (10 mL) was added. The organic layer was separated, the aqueous phase extracted with dichloromethane (2 × 20 mL) and the combined organic phases washed to neutrality with saturated aqueous ammonium chloride, then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/ether, 7:3) afforded 330 mg (71%) of nitrile **14**. − IR (film): ṽ = 3494, 3077, 2953, 2929, 2875, 2253, 1641, 1462, 1377, 1142, 1108, 1066, 993, 968, 912 cm^{-1}. − ^{1}H

NMR ($CDCl_3$): δ = 5.78 (ddt, J = 16.8, 9.9, 6.6 Hz, 1 H), 5.03 (d, J = 17.1 Hz, 1 H), 4.97 (d, J = 9.9 Hz, 1 H), 1.7−2.3 (m, 10 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.35 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 137.7, 120.8, 115.0, 83.0, 47.4, 41.8, 34.0, 30.1, 29.8, 27.2, 26.2, 26.0, 24.9, 22.5, 18.8. − $C_{15}H_{23}NO$ [M^+]: calcd. 233.1779; found 233.1781 (HRMS).

Aldehyde 15: A solution of diisobutylaluminium hydride (4.38 mL, 1 M in hexanes) was added dropwise to a solution of nitrile **14** (550 mg, 1.92 mmol) in ether (15 mL) cooled to 0°C. A solid rapidly precipitated. After stirring for 2 h at 0°C, methanol (2 mL) and a 0.7 M aqueous solution of potassium sodium tartrate (15 mL) were successively added. After stirring vigorously for 12 h and decantation, the organic layer was separated, the aqueous phase extracted with ether (2 × 10 mL) and the combined organic phases washed with brine (10 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/ether, 4:6) afforded 334 mg (100%) of aldehyde **14**. − IR (film): $\tilde{\nu}$ = 3481, 3076, 2954, 2876, 2748, 1682, 1641, 1460, 1376, 1287, 1252, 1190, 1105, 1065, 993, 952, 929, 912 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 9.42 (s, 1 H), 5.79 (ddt, J = 16.8, 10.2, 6.6 Hz, 1 H), 5.02 (d, J = 16.8 Hz, 1 H), 4.97 (d, J = 10.2 Hz, 1 H), 2.3−2.45 (m, 1 H), 2.09 (dt, J = 12.6, 6.6 Hz, 2 H), 1.7−2.0 (m, 6 H), 1.4−1.5 (m, 1 H), 1.52(s, 3 H), 1.48 (s, 3 H), 1.38 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 202.8, 137.9, 114.9, 84.2, 53.6, 49.8, 41.7, 35.6, 34.1, 30.0, 26.8, 26.5, 22.0, 20.8, 19.9. − MS (CI, NH_3); m/z (%): 219 (29) [M^+ − OH], 237 (37) [M^+ + H], 254 (2) [M^+ + NH_4]. − $C_{15}H_{24}O_2$ (236.35): calcd. C 76.23, H 10.23; found C 76.43, H 10.23.

Oxime 16: Sodium carbonate (895 mg, 8.45 mmol) and hydroxylamine hydrochloride (503 mg, 7.23 mmol) were successively added to a two-phase solvent system (dichloromethane/water, 3:1, 16 mL) containing aldehyde **15** (570 mg, 2.41 mmol). The reaction mixture was vigorously stirred for 4 days at room temperature. After decantation, the organic layer was separated and the aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with saturated aqueous ammonium chloride (10 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/AcOEt, 6:4) afforded 598 mg (99%) of oxime **16** as a 93:7 mixture of E and Z isomers; samples of the two isomers were separated. Z-Isomer − IR (film): $\tilde{\nu}$ = 3267, 3075, 2925, 1729, 1641, 1459 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 6.55 (s, 1 H), 5.78 (ddt, J = 16.8, 10.2, 6.6 Hz, 1 H), 4.99 (dd, J = 16.8, 1.5 Hz), 4.93 (dd, J = 10.2, 1.5 Hz, 1 H), 1.1−2.1 (m, 8 H), 1.46, (s, 3 H), 1.44 (s, 3 H), 1.13 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 153.6, 138.1, 114.7, 84.3, 41.9, 38.9, 34.2, 29.9, 29.4, 26.9, 26.6, 25.1, 20.9, 20.2. − MS (CI, NH_3); m/z (%): 234 (69) [M^+ − OH], 252 (100) [M^+ + H], 269 (15) [M^+ + NH_4]. − E-Isomer − IR (film): $\tilde{\nu}$ = 3308, 3076, 2926, 1723, 1640, 1456, 1376, 1302, 1260, 1187, 967, 910 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 8.6 (s, 1 H, NOH), 7.34 (s, 1 H), 5.77 (m, 1 H), 4.99 (d, J = 17.7 Hz, 1 H), 4.94 (d, J = 12 Hz, 1 H), 2.2−2.3 (m, 1 H), 2.0−2.1 (dt, J = 13.8, 6.6 Hz, 2 H), 1.2−2.0 (m, 7 H), 1.43, (s, 3 H), 1.38 (s, 3 H), 1.23 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 153.3, 138.1, 114.8, 84.3, 47.3, 41.8, 38.9, 34.3, 29.9, 26.9, 26.5, 25.1, 20.9, 20.2. − MS (CI, NH_3); m/z (%): 234 (100) [M^+ − OH], 252 (54) [M^+ + H].

Isoxazoline 3: To a solution of oxime **16** (327 mg, 1.3 mmol) in chloroform (2 L) was added a 7% solution of aqueous sodium hypochlorite (6.8 mL, 7.8 mmol). The reaction mixture was refluxed for 24 h; at this time oxime **16** was still present, so more of the solution of hypochlorite (3.4 mL, 3.6 mmol) was added, and heating was continued for a further 12 h. After cooling to room temperature, the organic phase was washed with brine (100 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/AcOEt, 1:1) afforded 265 mg (81%) of isoxazoline **3** (93:7 mixture of epimers) as a white solid. − m.p. 143.5−144°C. − IR (film): $\tilde{\nu}$ = 3421, 2923, 2871, 1602, 1455, 1372, 1302, 1185, 1150, 939, 839 cm^{-1}. − ^{1}H NMR ($CDCl_3$) of the major diastereomer: δ = 4.37 (dd, J = 8.1, 10.5 Hz, 1 H), 3.90 (dd, J = 6.9, 8.1 Hz, 1 H), 3.17 (dddd, J = 3.6, 6.9, 10.5, 12.3 Hz, 1 H), 2.35−2.20 (m, 1 H); 2.10−1.80 (m, 5 H), 1.65−1.20 (m, 5 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.10 (s, 3 H); characteristic peaks for the minor diastereomer: δ = 4.53 (dd, J = 8.6, 10.6 Hz, 1 H), 3.65 (dd, J = 8.6, 12.1 Hz, 1 H). − ^{13}C NMR ($CDCl_3$) of the major diastereomer: δ = 161.7, 84.1, 74.5, 52.7, 43.6, 39.8, 35.7, 33.4, 30.6, 28.9, 27.8, 27.3, 26.1, 25.8, 18.7. − MS (CI, NH_3); m/z (%): 232 (30) [M^+ − OH], 250 (100) [M^+ + H], 267 (80) [M^+ + NH_4]. − $C_{15}H_{23}NO_2$ [M^+]: calcd. 249.1729; found 249.1724 (HRMS).

Imines 17 and 18: To a solution of isoxazoline **3** (51 mg, 0.2 mmol) in methanol-water (5:1, 20 mL) were added boric acid (63 mg, 1 mmol) and Raney nickel (a spatula tip). The flask was fitted with a 3-way tap connected to a water aspirator and to a balloon filled with hydrogen. The flask was sequentially evacuated and filled with hydrogen. The suspension was vigorously stirred for 3 days at room temperature, then filtered through a short pad of celite, which was washed with methanol (20 mL). After concentration in vacuo, water (5 mL) and dichloromethane (15 mL) were added. After decantation, the organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over magnesium sulfate. After filtration and concentration in vacuo 50 mg of crude product were obtained. According to the ^{1}H NMR spectrum, it consisted of a mixture of imines **17** and **18**. A sample of imine **18** was isolated by chromatography on silica gel (AcOEt).

18: IR (film): $\tilde{\nu}$ = 3352, 2924, 2869, 1621, 1457, 1373, 1180, 1110, 936, 736 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 2.55−2.45 (m, 1 H), 2.21 (m, 1 H), 2.16 (m, 1 H), 2.1−1.2 (m, 9 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.03 (s, 3 H). − MS (CI, NH_3); m/z (%): 218 (80) [M^+ − OH], 236 (100) [M^+ + H].

17: This compound could not be purified since it decomposed during the column chromatography. It was mainly characterized owing to the occurrence of a signal in the ^{1}H NMR spectrum ($CDCl_3$): δ = 3.72 (d, J = 6.8 Hz, 3 H). The disappearance of this signal when the hydrogenation was continued was correlated with the increase of the intensity of the signal of the methyl group of compound **18** at δ = 1.11.

Isoxazoline 19: To a solution of isoxazoline **3** (22 mg, 0.09 mmol) in THF/water (2:1, 3 mL) was added amberlyst 15 (10 balls). The reaction mixture was stirred for 3.5 days at room temperature.The suspension was then filtered and the solid washed with dichloromethane (10 mL). Water (2 mL) was added, then the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were washed with water (2 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/AcOEt, 9:1) afforded 16 mg (72%) of isoxazoline **19**. − IR (film): $\tilde{\nu}$ = 3471, 2952, 2853, 1683, 1464, 1442, 1395, 1373, 1355, 1186, 1167, 953, 854, 737 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 4.15 (t, J = 8.1 Hz, 1 H), 4.11 (broad s, 1 H), 3.95 (dd, J = 8.1, 3.1 Hz, 1 H), 2.98 (m, 1 H), 2.35−2.7 (m, 3 H), 2.21 (dd, J = 16.2, 9.9 Hz, 1 H), 1.95 (t, J = 13.2 Hz, 1 H), 1.68 (s, 3 H), 1.3−1.9 (m, 5 H), 1.37 (s, 3 H), 1.19 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 169.3, 138.0, 136.4, 76.1, 75.0, 50.8, 40.4, 37.0, 33.9, 33.2, 29.4, 29.1, 26.9, 25.1, 13.8. − MS (CI, NH_3); *m/z* (%): 250 (100) [$M^+ + H$], 267 (18) [$M^+ + NH_4$]. − $C_{12}H_{17}NO$ [$M^+ - C_3H_6O$]: calcd. 191.1310, found 191.1300 (HRMS).

Isoxazolines 20 and 21: To a solution of isoxazoline **3** (20 mg, 0.08 mmol) in benzene (0.5 mL) was added dropwise a solution of (methoxycarbonylsulfamoyl)-triethylammonium hydroxide (Burgess reagent, 23.9 mg, 0.096 mmol) in benzene (1 mL). After stirring for 24 h at room temperature, more Burgess reagent (15 mg, 0.063 mmol) was added and the reaction mixture was refluxed for 2 h. After cooling to room temperature, water (2 mL) and dichloromethane (5 mL) were added. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were then washed with brine (5 mL) and dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (hexane/AcOEt, 9:1) afforded 10 mg (54%) of a 9:1 mixture of the inseparable isoxazolines **20** and **21**.

20: − IR (film): $\tilde{\nu}$ = 3088, 3039, 2922, 2853, 1636, 897, 839 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 4.95 (s, 2 H), 4.40 (dd, *J* = 7.8, 9.9 Hz, 1 H), 3.77 (dd, *J* = 7.8, 10.8 Hz, 1 H), 3.11 (m, 1 H), 2.52 (dt, *J* = 3.9, 12.3 Hz, 1 H), 1.5−2.3 (m, 9 H), 1.72 (s, 3 H), 1.68 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 166.2, 146.7, 136.8, 136.6, 113.3, 74.6, 52.3, 36.1, 35.6, 30.4, 29.4, 29.0, 25.9, 19.7, 13.7. − MS (CI, NH_3); *m/z* (%): 232 (100) [$M^+ + H$], 249 (75) [$M^+ + NH_4$].

21: − ^1H NMR ($CDCl_3$): δ = 5.25 (br. s, 1 H), 4.25 (dd, *J* = 8.2, 9.8 Hz, 1 H), 3.97 (dd, *J* = 8.0, 10.7 Hz, 1 H), 3.0−3.15 (m, 1 H), 2.43 (br. d, *J* = 17.9 Hz, 1 H), 2.37 (br. d, *J* = 17.9 Hz, 1 H), 1.64 (br. s, 3 H), 0.98 (s, 3 H).

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