Addition of Br_2 to Bicyclo[4.4.2]doceda-1,6-diene (21). Diene **21** (9.3 mg) was dissolved in 10 mL of dry CCl_4 in a foil-covered flask. To this was added 5% Br_2/CCl_4 (1.8 mL) via syringe (Br_2 color just persisted). The CCl_4 solution was filtered through Florisil and CCl_4 removed in vacuo to yield 0.030 g of viscous clear oil (**35**): ^1H NMR (80 MHz, $CDCl_3$) δ 4.13 (m, 1 H), 2.80–1.13 (m, 17 H); ^{13}C (62.9, $CDCl_3$) δ 79.5, 77.1, 64.1, 54.7, 49.3, 41.9, 37.9, 35.6, 34.7, 30.8, 25.5, 25.4; mass spectrum, *m/e* (CI, isobutane, 100 eV) 321 (MH^+), 241 ($MH^+ - 80$, $MH^+ - Br$); high-resolution mass spectrum, *m/e* (70 eV, EI) calcd (M^+) 319.9775, obsd (M^+) 319.9744.

Acknowledgment. We wish to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for financial support of this work. We also wish to thank Professor Robert Doedens for assistance with the X-ray crystal structure determination.

Supplementary Material Available: Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances (4 pages); tables of structure factors for dibromide **32** (3 pages). Ordering information is given on any current masthead page.

Convergent, Enantiospecific Total Synthesis of the Hypocholesterolemic Agent (+)-Compactin

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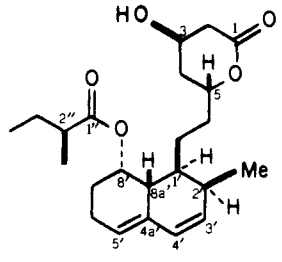
Abstract: A convergent, enantiospecific total synthesis of (+)-compactin (**1**) is described. The strategy for the construction of (+)-**1** centers around a Diels–Alder reaction between chiral dienophile **23** and chiral diene **62** which provides in a single operation access to allylic sulfide **85** possessing the desired configuration at C(8′), C(8a′), and C(1′). Dienophile **23** is made readily available by resolution of the known racemic β-nitro acid **66**. The synthesis of diene **62** commences with the known epoxide **7** derived from tri-*O*-acetyl-D-glucal. Diels–Alder adduct **85** is transformed into allylic alcohol **87** which sets the stage for incorporation of the C(2′) methyl group. Elaboration of the hexalol portion of compactin with liberation of the C(8′) hydroxyl group is achieved via a Grob-like fragmentation on alcohol **95**. Acylation of **94**, subsequent adjustment of the oxidation state at C(1), and demethylation give way to (+)-compactin.

Compactin (**1**), a fungal metabolite of *Penicillium brevicompactum*, was isolated in 1976 by Brown and co-workers.[1] Concurrently, Endo and co-workers[2] isolated a substance, ML 236B, from strains of *Penicillium citrinum* which proved to be identical with compactin. Compactin was first shown to have antifungal



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activity[1] but is best known for its hypocholesterolemic activity.[3] Compactin is a potent competitive inhibitor of the microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme in cholesterol biosynthesis.[4]

Compactin's unique structure which possesses a sensitive β-hydroxy lactone moiety and a hexahydronaphthalene unit containing four contiguous chiral centers [C(2′), C(1′), C(8a′), and C(8′)] makes it a synthetically challenging target. Since the disclosure that compactin is a potent competitive inhibitor of HMG-CoA reductase, it has been the object of intense synthetic activity. There have been numerous synthetic approaches to the hexahydronaphthalene fragment[10] and the β-hydroxy lactone portion[10b,11] of compactin. Simple synthetic analogues of compactin have also been described in the literature.[11a,b,12] The first

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(4) The major cause of death in the western hemisphere is coronary artery disease which is attributed in most cases to hypercholesterolemia.[5] The use of compactin has caused a marked decrease in serum cholesterol levels in rabbits, hens, dogs,[6] monkeys,[7] and humans.[8,9] Use of compactin or other hypocholesterolemic drugs may be a way to control or alleviate coronary artery disease.
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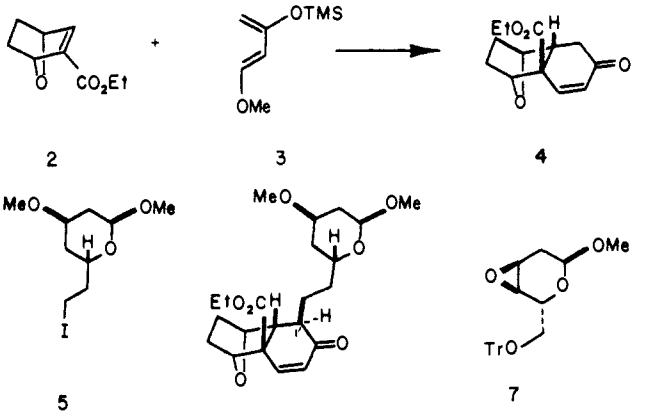
synthesis of compactin was reported in 1981 by Sih and coworkers.[13] Since the disclosure by Sih, several syntheses of compactin have been recorded.[14] We detail below an enantiospecific synthesis of (+)-compactin.[14c]

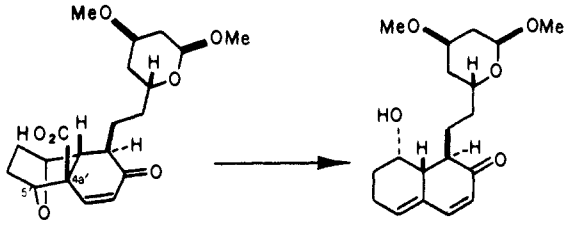
Results and Discussion

Preliminary Studies. Our initial strategy for the synthesis of compactin (**1**) centered on the use of enone **4** which, in principle, is readily available via an intermolecular Diels–Alder reaction between dienophile **2**[15] and Danishefsky's diene **3**.[16] It was



2 **3** **4** **5** **6** **7**

anticipated that alkylation of the enolate derived from enone **4** with a fully protected β-hydroxy lactone equivalent (cf. **5**) would give rise to enone **6**. Iodide **5** was expected to be available via carbohydrate chemistry. The known epoxy trityl ether **7**,[17] prepared previously from commercially available tri-*O*-acetyl-D-glucal, appeared to be the logical starting material for the preparation of iodide **5**. Decarboxylative elimination of the vinylogous β-keto acid **8** derived from **6** was expected to provide access to hexalone

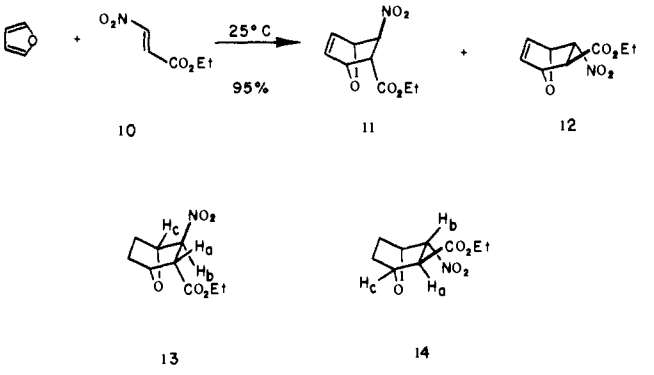


8 **9**

9 possessing three of the four contiguous chiral centers present in compactin. The requisite decarboxylative elimination requires that the dihedral angle between the carbonyl–C(4a′) bond and the C(5′)–oxygen bond be approximately 180° (i.e., antiperiplanar). A Newman projection about the C(4a′)–C(5′) bond clearly reveals the antiperiplanar arrangement of the carboxyl function and the oxygen atom.

Prior to embarking on a chiral synthesis of our starting dienophile **2**, we elected, during the very early stages of our synthetic studies, to employ racemic material for probing (1) the Diels–Alder reaction (**2** + **3** → **4**), (2) the alkylation of enone **4** with iodide **5**, and (3) the decarboxylative elimination of the vinylogous β-keto acid **8**.

The preparation of dienophile **2** follows from the work of Just.[18] Condensation of furan with ethyl β-nitroacrylate (**10**)[19] afforded a 95% yield of adducts **11** and **12** as a mixture. This mixture



10 **11** **12** **13** **14**

is of no consequence since after elimination of nitrous acid both centers become sp^2 hybridized. It was found, however, that the ratio of **11**:**12** varied depending on reaction time. For example, after 26 h at room temperature the ratio of endo nitro adduct **11** to exo nitro adduct **12** was 1.5:1.0 as evidenced by ^1H NMR analysis. If, on the other hand, the reaction was allowed to proceed for 60 h, the ratio of **11**:**12** changed to 4.0:1.0, however, still in favor of **11**. Similar results have been reported by both Just[20] and Koning[21] on analogous systems. Separation of **11** and **12** was easily achieved by column chromatography, thus permitting complete characterization of each adduct.

Adduct **11**, mp 52–53 °C, upon reduction using hydrogen and 10% palladium on carbon in absolute ethanol afforded nitro ester **13**, mp 35–36 °C, in 95% yield. The 220-MHz NMR spectrum of **13**, which reveals H_a as a doublet (δ 3.34) with J_{ab} = 4.5 Hz and H_b as a doublet of doublets (δ 5.27) with J_{ba} = 4.5 and J_{bc} = 5.0 Hz, is completely in accord with the structure assigned to adduct **11**.[22]

Similarly, adduct **12** was reduced (H_2, 10% Pd/C, absolute ethanol), giving rise to nitro ester **14** in 94% yield. The 220-MHz NMR spectrum of **14** displayed H_a as a broad triplet (δ 3.77) with $J_{ab} = J_{bc}$ = 5.0 Hz and H_b as a doublet (δ 5.03). For convenience, reduction of adducts **11** and **12** was usually run directly on the mixture obtained from the Diels–Alder reaction. There was no observable reduction of the nitro group to the amine under the above conditions. However, attempted reduction (H_2, Pd/C) of adducts **11** and **12** in quantities greater than ca. 2 g led to a very slow reaction or no reaction at all. To alleviate this problem, large-scale reductions of **11** and **12** were performed using in situ generation of diimide.[23] Treating a stirred suspension of adducts **11** and **12** in the presence of potassium azodicarboxylate in absolute methanol with acetic acid at 0 °C followed by warming to room temperature provided nitro esters **13** and **14** in 95% yield.[15] Subsequent treatment of the mixture of nitro esters **13** and **14** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing benzene for 5 min afforded dienophile **2**, as a volatile substance, in 80% yield.

Treatment of racemic dienophile **2** with 2.15 equiv of Danishefsky's diene **3** in refluxing toluene for 4.5 h followed by hydrolysis afforded enone **4** and a mixture of β-methoxy ketones **16** in 94% yield. The ratio of **4**:**16** varied depending upon the conditions used to hydrolyze the intermediate silyl enol ether **15**. Employing tetrahydrofuran and 0.1 N hydrochloric acid (4:1) provided **4** and **16** in a ratio of 2.2:1.0. In contrast, use of 0.005

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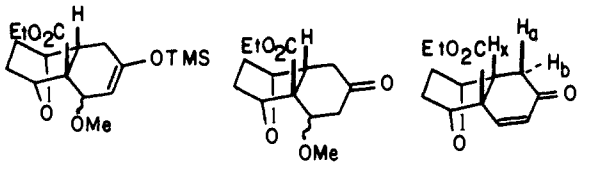


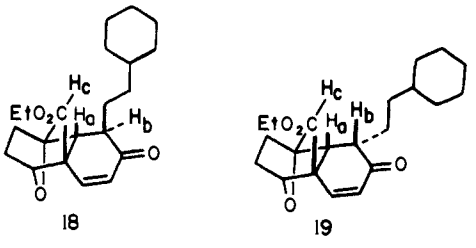
15 16 4

N hydrochloric acid in tetrahydrofuran (1:4) gave a 5.6:1.0 ratio of **4**:**16**. Similar observations have been recorded in the literature.[16]

Intermediate adduct **15** results from endo addition of diene **3** to the exo face of dienophile **2**. Verification of the structure assigned to enone **4**, mp 74.5–75 °C, follows from the infrared spectrum (1730, 1685 cm^{-1}) as well as its 220-MHz NMR spectrum. The NMR spectrum of enone **4** displayed H_a and H_b as an AB portion of an ABX system centered at δ 2.34 with J_{ab} = 15.0, J_{ax} = 8.0, and J_{bx} = 2.5 Hz.

The mixture of β-methoxy ketones **16** was smoothly transformed into enone **4** by exposure to 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing toluene. For convenience the products **4** and **16** from the Diels–Alder reaction were not separated but directly treated with DBU in refluxing toluene to afford enone **4** exclusively. With an efficient route to enone **4** available, attention was focused on alkylation adjacent to the ketone functionality with a suitable β-hydroxy lactone equivalent. Preliminary studies were carried out employing the readily available iodide **17**. Treating

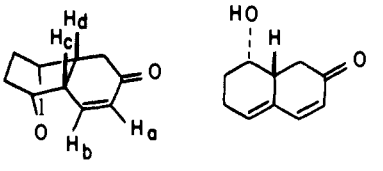
17



18 19

enone **4** with lithium diisopropylamide in tetrahydrofuran containing hexamethylphosphoramide at 0 °C followed by adding 1.5 equiv of iodide **17** and subsequent warming to room temperature led to a 7:3 mixture of enones **18** and **19** in 18% yield. Starting enone **4** was recovered in 26% yield. The structures assigned to the alkylated products follow from their 220-MHz NMR spectra. The NMR spectrum of enone **18** revealed H_a as a singlet (δ 2.80), which is in keeping with the fact that the dihedral angle between H_a and H_b as well as between H_a and H_c is ca. 90°. On the other hand, enone **19** displayed H_a as a doublet (δ 2.97) with J_{ab} = 7.0 Hz. All attempts to improve the yield of **18** and **19** by playing with reaction conditions failed. The low yield associated with the above alkylation reaction is attributed to the severe steric congestion on both faces of the enolate derived from **4**. The carboethoxy group hinders approach of the reagent from the β face, whereas the oxa bridge hinders attack from the α face. Attempts using either the tosylate or triflate derived from cyclohexylethanol led to production of numerous unidentifiable products. Use of the potassium enolate derived from **4** gave a disappointingly low yield of the desired alkylation product.

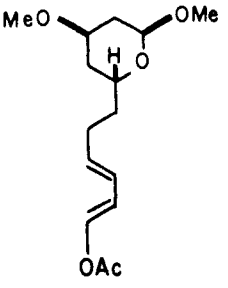
Concurrent with the above alkylation study, we examined the decarboxylative elimination of enone **4**. Upon treatment of **4** with sodium chloride in aqueous dimethyl sulfoxide at ca. 180 °C for 9 h, enone **20**, mp 81.5–83.0 °C, was isolated in 20% yield along with 20% recovered starting enone. That elimination of the oxa bridge had not occurred was clearly evident from the NMR



20 21

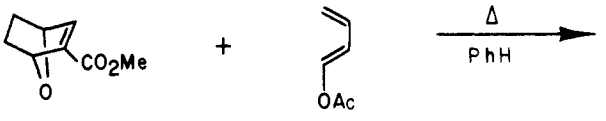
spectrum which revealed H_a as a doublet (δ 5.90) with J_{ab} = 10 Hz and H_b as a doublet of doublets (δ 6.55) with J_{bc} = 4.0 and J_{ba} = 10.0 Hz. In contrast, exposure of enone **4** to barium hydroxide hexahydrate in 95% ethanol at 100 °C for 2 h gave a 1:1 mixture of **20** and **21** in ca. 16% yield. The structure of **21** was fully supported by its spectral data. Attempts to further improve the yield of the decarboxylative elimination were unsuccessful. These results along with the disappointingly low yields experienced above in connection with the alkylation studies prompted us to seek alternate routes to compactin.

Another approach, which appeared to offer hope in terms of overcoming the difficulties encountered above with respect to the alkylation of **4**, centered around incorporating the carbohydrate-derived component into the diene unit (cf. **22**). However,

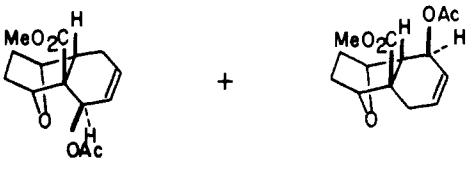


22

prior to embarking on a synthesis of **22** we examined in a preliminary study the reaction of **23** with 1-acetoxy-1,3-butadiene (**24**) in refluxing benzene. HPLC analysis of the reaction mixture revealed a 95:5 mixture of Diels–Alder adducts **25** and **26** which could be isolated in 83% yield.



23 24



25 26

In view of the fact that allylic carbamates in which the nitrogen bears a hydrogen have been shown to undergo addition with lithium dimethylcuprate in a syn S_N2' fashion,[24] acetate **25** was converted in a straightforward manner [(1), K_2CO_3, MeOH; (2) PhNCO, PhH, reflux (95% overall)] into carbamate **27**. Reaction of allylic carbamate **27** with lithium dimethylcuprate or lithium cyanomethylcuprate[25] gave rise after several attempts to only recovered **27**. It has been suggested[24b] that the addition of cuprates to allylic carbamates proceeds via a mixed cuprate **28** which undergoes intramolecular oxidative addition to the γ-sp^2-hybridized

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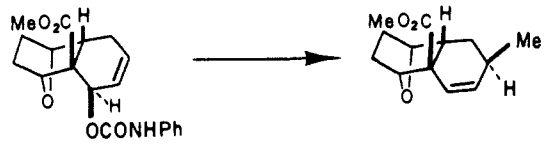
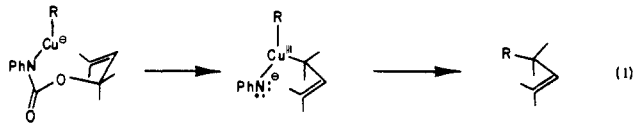


27 31

carbon (eq 1), giving rise to a copper(III) σ-allyl complex, **29**.

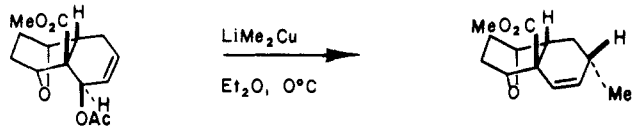


(1)

28 29 30

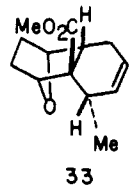
Reductive elimination converts **29** into **30**, the product of syn γ-alkylation. After the fact, it is not surprising that substrate **27** did not give rise to the syn γ-alkylated product **31** since the rigidity of the molecule and the severe steric hindrance about C(4′) inhibit the proper orientation of the carbamate functionality.

Disappointed by our inability to introduce a methyl group into the C(2′) position via carbamate **27**, we nonetheless examined the reaction of allylic acetate **25** with lithium dimethylcuprate realizing



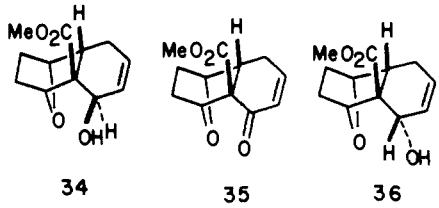
25 32

full well that the reaction would proceed in an anti S_N2' fashion[26] giving rise to the wrong configuration at C(2′) (cf. **25** → **32**). Indeed, reaction provided an 80% yield of a single substance, **32**, having the undesired configuration at C(2′). The absence of α-substituted product **33** was anticipated in view of the neopentyl nature of the C(4′) carbon.



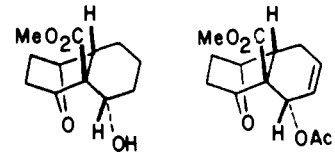
33

In order to realize the proper orientation of the methyl group at C(2′) (cf. **31**), the acetate at C(4′) in **25** was inverted prior to the cuprate reaction. Toward this end, Swern oxidation of allylic alcohol **34** gave rise to enone **35** which upon reduction with sodium



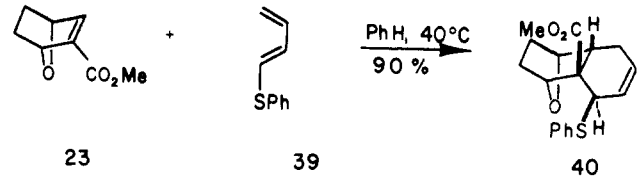
34 35 36

borohydride–cerium chloride in methanol[27] afforded exclusively allylic alcohol **36**. Reduction of **35** with sodium borohydride in the absence of cerium chloride generated saturated alcohol **37** as the product. Acetylation of **36** provided allylic acetate **38** which upon exposure to lithium dimethylcuprate gave rise to **31** in 70% overall yield. That the assignment of configuration at C(2′) was correct as shown follows from comparison of the spectra of **31** with those obtained from a sample of **31** prepared by an alternate route.[28]



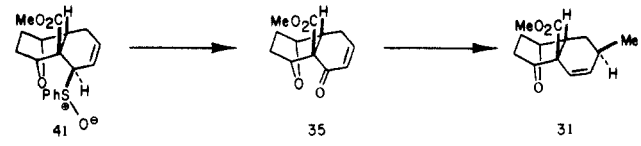
37 38

While the above model studies were in progress it was simultaneously found that dienophile **23** undergoes Diels–Alder reaction with 1-(phenylthio)-1,3-butadiene (**39**), giving rise to adduct **40** in 90% yield. In principle the intermediate allylic sulfide

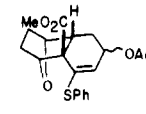


23 39 40

40 offers a number of possibilities for transformation into **31** via the corresponding sulfoxide **41**. It was anticipated that Pummerer rearrangement of sulfoxide **41** would give rise to the known enone



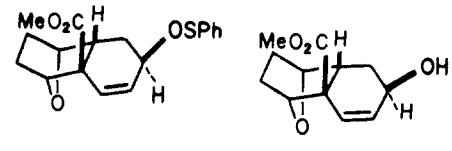
41 35 31



42

35 (vide supra) directly or indirectly via vinyl sulfide **42**. Alternately, it is known[29] that allylic sulfoxides react in a S_N2' fashion with lithium dimethylcuprate; however, the mode of attack, syn vs. anti, has not as yet been established. In order to probe this latter possibility, Diels–Alder adduct **40** was oxidized with *m*-chloroperbenzoic acid at −78 °C.

Much to our surprise, none of the desired allylic sulfoxide **41** could be detected; however, a 90% yield of allylic sulfenate **43** was isolated. The exclusive formation of sulfenate **43** undoubtedly stems from severe steric interactions between the phenylsulfinyl group at C(4′) and the carbomethoxy group at C(4a′). Treatment of **43** with trimethyl phosphite in refluxing methanol afforded allylic alcohol **44** in 92% yield.



43 44

Since it was not known what effect placing an alkyl substituent at C(1′) in sulfoxide **41** would have on the allylic sulfoxide–sulfenate equilibrium, the preparation of a model system to examine this question was undertaken. Diels–Alder reaction of dienophile **23** with diene **45**[30] afforded a 4:1 mixture of adducts **46** and **47**, respectively, in 77% yield. Crystallization from pentane provided pure adduct **46**, mp 69.0–70.5 °C. The stereochemical assignment of adduct **46** follows from its NMR spectrum which

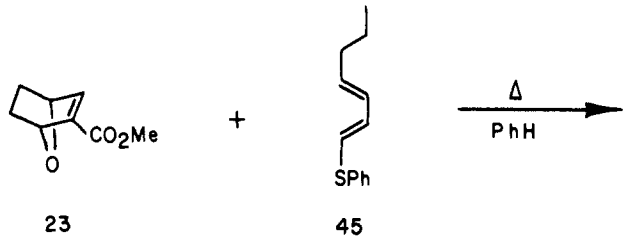
(26) (a) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854. (b) Rona, R.; Tokes, L.; Tremble, J.; Crabbé, P. *J. Chem. Soc. D* **1969**, 43.

(27) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

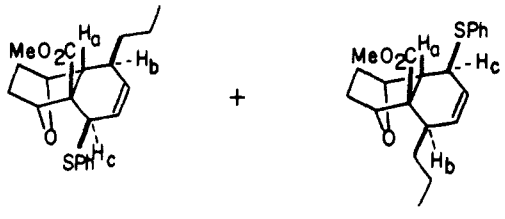
(28) Robert Zelle, Indiana University, unpublished results.

(29) Masaki, Y.; Sakuma, K.; Kaji, K. *J. Chem. Soc., Chem. Commun.* **1980**, 434.

(30) Prepared via Wittig reaction of *trans*-2-hexenal with the anion of diphenyl((phenylthio)methyl)phosphine oxide; cf.: Grayson, J. I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263 and references cited therein.



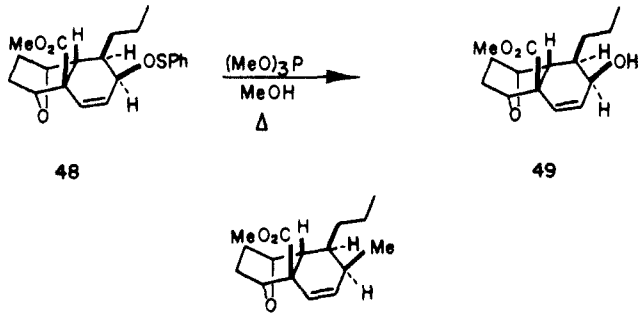
23 45



46 47

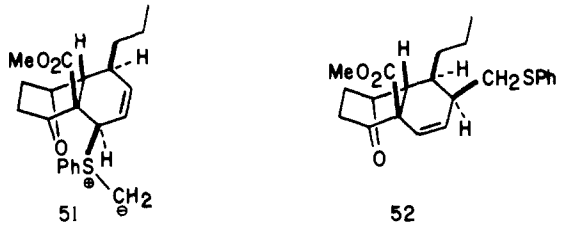
reveals H_a as a doublet centered at δ 2.11 and J_{ab} = 9.5 Hz and H_c as a broad singlet located at δ 3.90 due to very small vicinal and allylic couplings.

Oxidation of sulfide **46** afforded allylic sulfenate **48** which was smoothly transformed into allylic alcohol **49** in 70% overall yield. Unfortunately, the formation of **49** from **46** does not permit direct



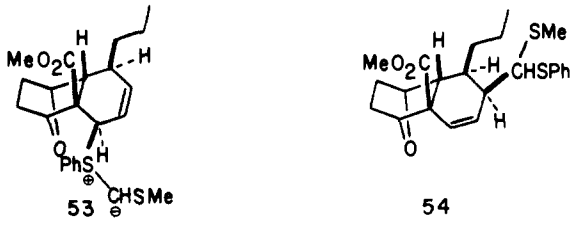
48 49 50

elaboration into the desired C(2′) methyl compound **50** since this would require replacing the hydroxyl by a methyl with retention. In view of the availability of allylic sulfide **46** and the facile manner in which the derived sulfoxide underwent smooth [2,3]-sigmatropic rearrangement, we set out to examine several options for elaboration of **46** into **50**. In principle formation of sulfur ylide **51** from



51 52

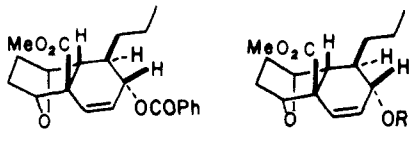
46 should give rise to rearranged homoallylic sulfide **52** and hence **50** upon Raney nickel desulfurization. Treatment of Diels–Alder adduct **46** with a solution of diethylzinc and methylene iodide in anhydrous benzene according to the procedure of Cohen[31] afforded none of the desired rearranged homoallylic sulfide **52**. Similarly, treatment of **46** with (trimethylsilyl)methyl triflate in dry acetonitrile followed by anhydrous cesium fluoride[32] gave none of the desired sulfide **52**. Attempts to prepare ylide **53**, a potential precursor to the rearranged system **54**, were also unsuccessful,



53 54

in part due to the inability to obtain the necessary sulfonium salt from reaction of **46** with either chloromethyl methyl sulfide or iodomethyl methyl sulfide.

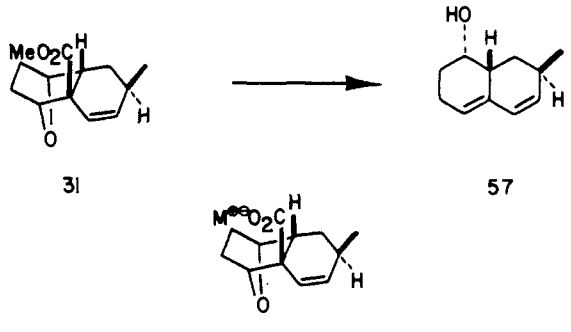
Having been uniformly unsuccessful in our efforts to develop a direct route for introduction of the C(2′) methyl group, attention was refocused on converting allylic alcohol **49** into **50**. Toward this end, alcohol **49** was subjected to a Mitsunobu reaction[33] which provided in 94% yield allylic benzoate **55**. In principle the allylic



55 56

benzoate should be a prime candidate for S_N2 displacement with lithium dimethylcuprate. However, all attempts to react **55** with lithium dimethylcuprate or lithium cyanomethylcuprate gave rise to only recovered starting material. Cleavage of benzoate **55** afforded alcohol **56** (R = H) which upon acetylation gave acetate **56** (R = Ac) in 81% overall yield. Treatment of allylic acetate **56** (R = Ac) with lithium dimethylcuprate provided **50** in 70% yield. The NMR (360-MHz) spectrum of **50** revealed H_a and H_b as the AB portion of an ABX system (δ 5.91) with J_{ab} = 9.7 and J_{ax} = 5.0 Hz and H_c as a doublet (δ 2.45) with J_{cd} = 9.0 Hz. The C(2′) methyl portions appeared as a doublet (δ 0.84) with J = 6.9 Hz. The NMR data obtained for **50** are analogous to those obtained for substrate **31**.[28]

Having achieved stereoselective syntheses of **31** and **50**, our efforts were once again redirected to the transformation of substrates such as **31** and **50** into their corresponding hexalols (cf. **31** → **57**). Treatment of **31** with sodium hydroxide afforded the



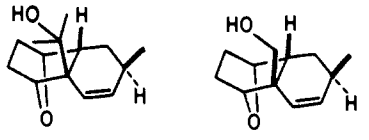
31 57 58

crystalline carboxylate salt **58** (M^+ = Na^+) which upon heating in refluxing xylene afforded only recovered starting material. Similar results were obtained with the barium, cesium, potassium, and thallium salts. The inability of **58** to lose carbon dioxide can be attributed to the fact that decarboxylation ultimately leads to an oxygen–carbon–oxygen bond angle of 180°. Nonbonded steric interactions with the endo protons of the oxabicyclo[2.2.1]heptane portion of the molecule may not allow this linearity to be achieved in the transition state.[34]

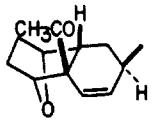
An alternate approach via a Grob-like fragmentation was examined. Treatment of ester **31** with methyllithium in tetrahydrofuran afforded a near quantitative yield of a 1:1 mixture

(31) (a) Cohen, T.; Kosarych, Z. *J. Org. Chem.* **1982**, *47*, 4005. (b) Kosarych, Z.; Cohen, T. *Tetrahedron Lett.* **1982**, 3019.
(32) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
(33) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427.
(34) Cf.: May, D. D.; Skell, P. S. *J. Am. Chem. Soc.* **1982**, *104*, 4500.

of tertiary alcohol **59** and methyl ketone **60**, which were readily



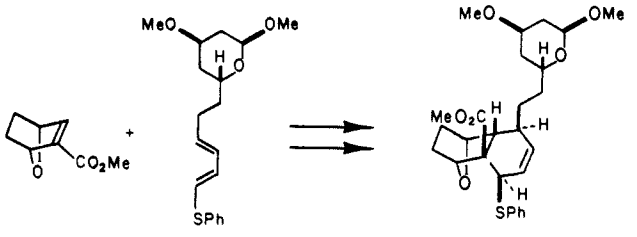
59 **61**



60

separated by column chromatography. The methyl ketone could be recycled by further treatment with methyllithium. Exposure of tertiary alcohol **59** to potassium hydride in refluxing tetrahydrofuran provided the desired product **57** in 90% yield (50% conversion). In contrast the corresponding alcohol **61**, obtained by reduction of **31** with lithium aluminum hydride, upon treatment with potassium hydride under identical conditions led only to recovery of starting material.

Encouraged by the results of the preliminary model studies described above, efforts were refocused on the task of preparing compactin by total synthesis. The strategy for the construction of compactin centered around the Diels–Alder reaction between optically active dienophile **23** and optically active diene **62**.

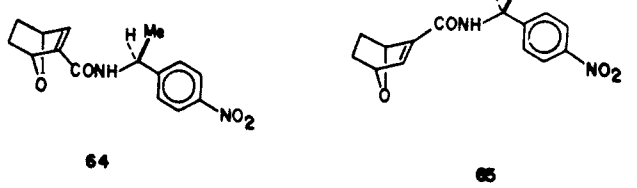


23 **62** **85**

Synthesis of Dienophile 23 in Chiral Form. Since dienophile **23** was readily available in racemic form in excellent overall yield, an attempt was made to resolve **23**. Initial efforts centered around preparing a number of diastereomeric amides from **23** by using chiral amines. Separation of the diastereomers by preparative LC and subsequent hydrolysis would provide each diastereomer in optically pure form.[35]

To this end, racemic **23** was saponified by using 10% potassium hydroxide solution in tetrahydrofuran. Acidification afforded in quantitative yield the corresponding racemic acid.[15] Subsequent treatment with oxalyl chloride in benzene containing *N,N*-dimethylformamide produced the desired acid chloride **63**. Exposure of **63** to a number of chiral amines [(−)-α-phenylglycinol, (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol, *l*-(−)-(*p*-nitrophenyl)ethylamine, and *l*-(−)-(α-naphthyl)ethylamine] led to mixtures of diastereomers. Diastereomers **64** and **65**, obtained from *l*-(−)-(*p*-nitrophenyl)ethylamine, gave rise to the best selectivity factor (α).[36] A quantitative separation of **64** and **65** could be realized on a Waters Prep LC/System 500A, provided that less than 1 g of the diastereomeric mixture was used.

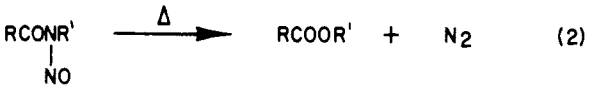
63



64 **65**

Hydrolysis of **64** and **65** was attempted employing several methods (10% H_2SO_4 in MeOH, 14% $HClO_4$ in MeOH, and 48% HBr); however, no hydrolysis was observed at room temperature. Under refluxing conditions, numerous products were produced. Hydrolysis was finally accomplished by treatment of the mixture of amides **64** and **65** with dinitrogen tetroxide in carbon tetrachloride[37] and subsequent exposure to methanolic sodium methoxide. The overall yield for the hydrolysis sequence was ca. 40%, far from being satisfactory.

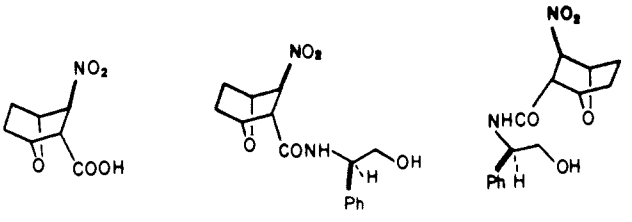
White[38] has shown (eq 2) that *N*-nitrosoamides thermally rearrange, giving rise to nitrogen and esters in excellent yield. Following the procedure of White,[38] *N*-nitrosoamides **64** and **65**



(2)

were refluxed in carbon tetrachloride and subsequently treated with methanolic sodium methoxide, giving rise to **23** in 76% yield, thus improving the overall yield for the hydrolysis sequence to 55%. Efforts to improve the yield of the nitrosation step by treating **64** and **65** with nitrosonium tetrafluoroborate[39] in dry acetonitrile led to the formation of numerous products. The inability to separate more than 1 g of **64** and **65** at any one time by preparative LC, coupled with the poor yields associated with the hydrolysis sequence, suggested that an alternate way to perform the resolution would be necessary.

Resolution was accomplished finally by working with the β-nitro acid **66**[15] derived from ester **13**. Saponification of ester **13** provided in 97% yield carboxylic acid **66**. Interestingly, no β-elimination



66 **67** **68**

products were observed during the hydrolysis.[15] Coupling of racemic **66** with a number of chiral amines [(−)-α-phenylglycinol, *l*-(−)-(*p*-nitrophenyl)ethylamine, *l*-(−)-(α-naphthyl)ethylamine, and *l*-(−)-methylbenzylamine] was achieved by using dicyclohexylcarbodiimide in anhydrous methylene chloride. Amides **67** and **68** derived from D-(−)-α-phenylglycinol exhibited the best α value. Quantitative separations could be realized on a 10-g scale in a single pass through a Waters Prep LC/System 500A. This result was especially pleasing since it was anticipated that the presence of the hydroxyl group in the amide would assist in the hydrolysis step via intramolecular esterification.[35]

Assignment of each amide follows from a single-crystal X-ray analysis of an advanced intermediate in the synthesis (vide infra). Amides **67** and **68** were unstable and were directly hydrolyzed after separation. Hydrolysis of the less polar amide **67** afforded optically pure nitro ester **69** ($[\alpha]_D$ −82.6° (*c* 3.05, $CHCl_3$)) in 48% yield from racemic acid **66**. Similarly, the more polar amide **68** gave rise to nitro ester **70** ($[\alpha]_D$ +78.5° (*c* 3.78, $CHCl_3$)) in 48%

(35) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63.

(36) Determined on a Waters Analytical HPLC system using a μ-Porasil (P/N 27477 S/N) column.

(37) Reimlinger, H. *Chem. Ber.* **1961**, *94*, 2547.

(38) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6011.

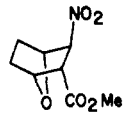
(39) Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1965**, *30*, 2386.

Table I. Reductive Ring Opening of Epoxide 7

hydride	solvent	temp/°C	ratio 72:73
$LiAlH_4$	Et_2O	−10	1:1
$LiAlH_4$	THF	0	1.4:1.0
$LiEt_3BH$	THF	−22 → 0	1.0:2.0
AlH_3	Et_2O	−10	1.0:1.0

yield from **66**. Elimination of nitrous acid from nitro ester **69** provided optically pure ester **23** ($[\alpha]_D$ +179.35° (*c* 1.88, $CHCl_3$)) in 75% yield.

During the course of this study, it was discovered[15] that the isomeric β-nitro ester **14** upon treatment with potassium hydroxide followed by acidification gave rise to a 91% yield of **66** and **71** in a ratio of 5.2:1.0, thus allowing for recycling of the minor Diels–Alder adduct **12**.



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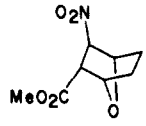

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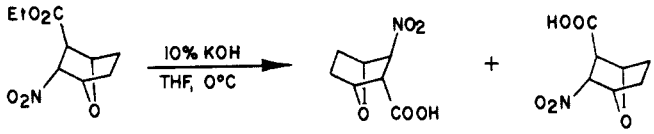
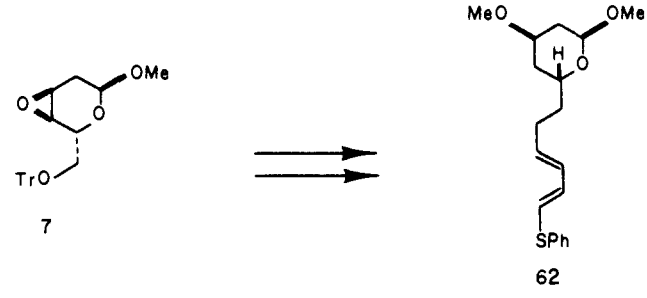


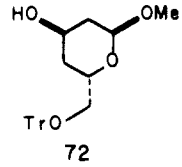
14 66 71

Synthesis of Diene 62. Construction of diene 62 in optically pure form commenced with epoxy trityl ether **7** which had previously been prepared[17] from commercially available tri-*O*-acetyl-D-glucal. Opening of the epoxide function in **7** using

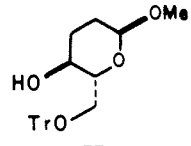


7 62

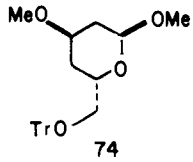
lithium aluminum hydride in ether gave an 11:1 mixture of alcohols **72** and **73**, respectively, in 98% yield. The mixture could not be separated by column chromatography; however, alcohol **72** crystallized exclusively from ether–hexane. Other reducing agents gave rise to quite different ratios of **72** and **73** (Table I).



72



73



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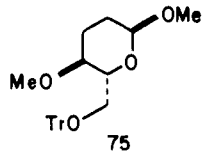
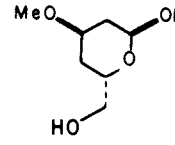


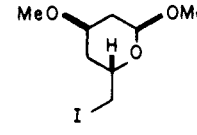
75

Dramatic solvent effects were also observed. For example, replacing ether by tetrahydrofuran in the lithium aluminum hydride reduction resulted in a complete loss of selectivity.

Alcohol **72** was protected as a methyl ether primarily due to its stability under a broad range of reaction conditions. For convenience the above mixture of **72** and **73** was converted into methyl ethers **74** and **75** since both **74** and **75** could be easily separated by column chromatography. Detritylation of **74** was accomplished by treatment with sodium in liquid ammonia, affording alcohol **76** in 79% yield. Conversion of alcohol **76** into



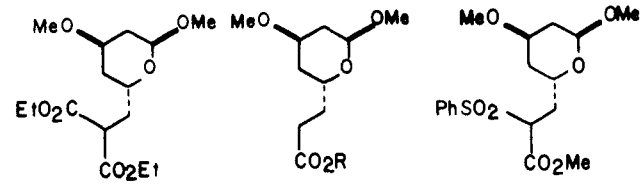
76



77

iodide **77** was carried out via a two-step process. Tosylation proceeded uneventfully, affording the corresponding tosylate which was directly treated with sodium iodide in refluxing methyl ethyl ketone. Iodide **77** was thus obtained in 92% overall yield.

Treatment of iodide **77** with sodium diethylmalonate in absolute ethanol at reflux generated malonate **78** in 87% yield. Several unsuccessful attempts were made to obtain mono ester **79** (R = Et) via decarboxylation. Heating malonate **78** with sodium



78 79 80

chloride in wet dimethyl sulfoxide[40] at ca. 180 °C produced a number of unidentified products. Use of basic alumina in refluxing wet dioxane[41] led only to recovery of **78**. Attempted decarboxylation on the corresponding diacid was also unsuccessful. The above problems were alleviated by alkylation of iodide **77** with the carbanion derived from methyl (phenylsulfonyl)acetate in dimethyl sulfoxide. A 90% yield of sulfone **80** was realized which was smoothly desulfonylated with 6% sodium amalgam in methanol,[42] giving rise to **79** (R = CH_3) in 92% yield. Treatment of sulfone **80** with either aluminum amalgam in aqueous tetrahydrofuran or calcium in liquid ammonia led to inferior yields of ester **79** (R = CH_3).

Reduction of ester **79** (R = CH_3) with lithium aluminum hydride afforded alcohol **81** in quantitative yield. Collins oxidation of **81** provided the sensitive aldehyde **82** (90% yield) which was immediately condensed with [(trimethylsilyl)propargylidene]-triphenylphosphorane,[43] giving rise to enyne **83** in 82% yield as a 9:1 mixture of *E* and *Z* isomers. No attempts were made to separate this mixture since the *Z* isomer was not expected to participate in the Diels–Alder reaction. Desilylation of **83** was accomplished by treatment with tetra-*n*-butylammonium fluoride which afforded enyne **84** in quantitative yield. Radical addition[44] of thiophenol to the terminal acetylene of **84** generated diene **62** in 94% yield as a 3:2 mixture of *E* and *Z* isomers about the vinyl sulfide carbon–carbon double bond. This ratio was determined from a 220-MHz NMR spectrum. Attempted isomerization of diene **62** with iodine in carbon tetrachloride was unsuccessful. No effort was made to separate this mixture of (*E*)- and (*Z*)-olefins

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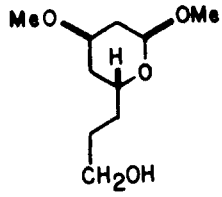

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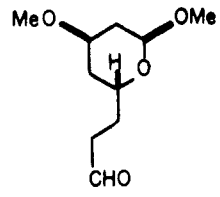

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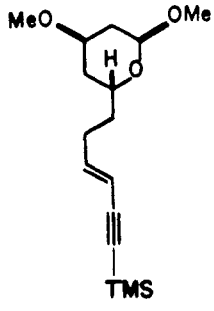

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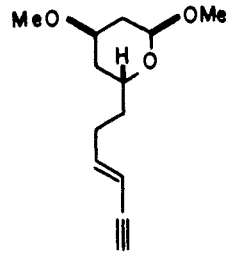
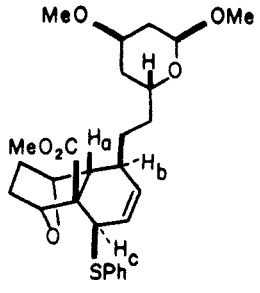


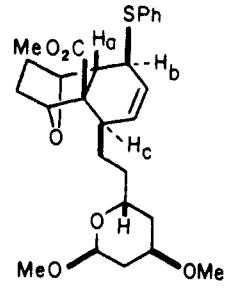
84

since it was shown (vide infra) that under the thermal conditions of the Diels–Alder reaction the *Z* isomer equilibrates to the *E* isomer as the *E* isomer is being consumed.

Completion of the Synthesis of Compactin. With both dienophile **23** and diene **62** available in enantiomerically pure form, the stage was set for the construction of the carbon framework of compactin. Heating a mixture of diene **62** and dienophile **23** in toluene afforded Diels–Alder adducts **85** and **86** in 86% yield as a 7:3



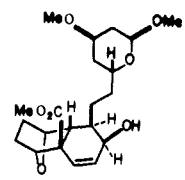
85



86

mixture, as determined by HPLC analysis. The extreme volatility of **23** necessitated that the reaction be conducted in a sealed tube. Separation of the adducts was accomplished by analytical HPLC. The stereochemical assignments follow from the NMR (360-MHz) spectra of **85** and **86**. The spectrum of the desired regioisomer **85** reveals H_a as a doublet (δ 2.14) with J_{ab} = 9.5 Hz and H_c as a broad singlet (δ 3.85). In contrast the NMR spectrum of **86** displayed H_a as a sharp doublet (δ 2.35) with J_{ab} = 9.5 Hz and H_b as a broad doublet centered at δ 3.48. Note that the lack of diastereoisomers related to **85** is due to an inherent bias of the system. The Diels–Alder reaction between **23** and **62** can only proceed via endo addition of the diene to the exo face of the oxabicyclo[2.2.1]heptene ring system.

Oxidation of allylic sulfide **85** with *m*-chloroperbenzoic acid gave way directly to the corresponding rearranged allylic sulfenate as anticipated on the basis of previous observations. Treatment of the sulfenate with trimethyl phosphite in methanol led to the isolation of allylic alcohol **87** in 80% overall yield from **85**. For practical purposes, the mixture of **85** and **86** need not be separated since application of the oxidation–rearrangement–cleavage sequence directly on the mixture of **85** and **86** leads in 60% isolated yield to **87**. None of the isomeric allylic alcohol **88** could be detected, which suggests that under the reaction conditions, allylic



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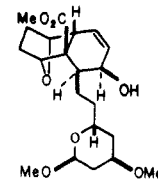

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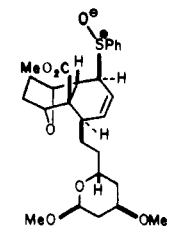
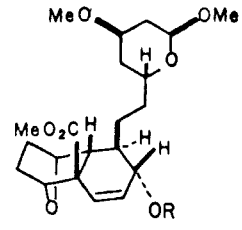


89

sulfoxide **89** is not in equilibrium with the corresponding allylic sulfenate.

Allylic alcohol **87** was subjected to a Mitsunobu reaction.[33] Inversion of configuration about C(2′) proceeded smoothly, giving rise to **90** (R = COPh) in 93% yield. Cleavage of the benzoate with methanolic sodium methoxide afforded alcohol **90** (R = H)



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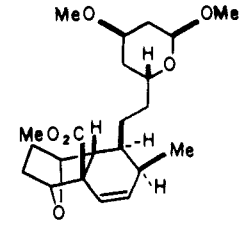


91

as a crystalline compound, mp 124.0–125.0 °C, in 85% yield. The structure of **90** (R = H) was unambiguously established by single-crystal X-ray analysis.[45] Acetylation of **90** (R = H) gave a quantitative yield of acetate **90** (R = Ac). Several attempts were made to obtain acetate **90** (R = Ac) directly from alcohol **87** by substituting dry acetic acid for benzoic acid in the Mitsunobu reaction. Unfortunately, the desired acetate was only formed in modest yield (46%).

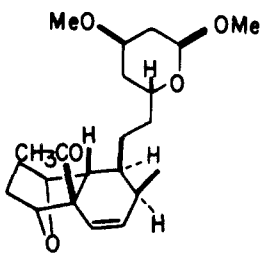
Treatment of acetate **90** (R = Ac) with lithium dimethylcuprate gave rise exclusively to olefin **91** in 86% yield. With the configuration at C(2′) established, it was anticipated that the conversion of olefin **91** into compactin would proceed smoothly, taking advantage of the model systems examined previously.

Toward this end, ester **91** was treated with methyllithium, giving rise to ketone **92** as the sole product in 91% yield. Reduction of **92** with lithium aluminum hydride produced alcohol **93** as a 3:1 mixture of diastereomers in 98% yield. Treatment of **93** with potassium hydride in refluxing toluene generated dienol **94** (12%) along with recovered starting material (20%). In view of the poor yield obtained in the formation of dienol **94**, other avenues were examined. Reduction ($LiAlH_4$) of ester **91** afforded primary alcohol **95** in 98% yield. Treatment of **95** with potassium hydride in refluxing toluene gave dienol **94** in 40% yield (50% based on recovered **95**).

With the four contiguous chiral centers [C(2′), C(1′), C(8a′), and C(8′)] established in the hexalol portion of compactin, attention was focused on completion of the total synthesis which required (1) acylation of the C(8′) hydroxyl, (2) adjustment of the oxidation state at C(1), and (3) cleavage of the methyl ether. Alcohol **94** was treated with (*S*)-2-methylbutyric anhydride[46] and

(45) Compound **90** (R = H) crystallizes in space group $P2_1$ with cell dimensions (at −164 °C) a = 11.748 (3) Å, b = 7.502 (1) Å, c = 12.444 (3) Å, β = 105.60 (1)°, V = 1030.86 Å^3, and c = 1.277 g cm^{-3} (for Z = 2). A total of 6748 reflections were measured, of which 3666 were determined to be observable ($F_o < 2.33(F_o)$). The structure was solved by using a straightforward NQUEST approach by D. Langs (Medical Foundation of Buffalo). A Picker four-cycle goniostat equipped with a Furnas monochromator was used (for experimental methods and data reduction details, see: Huffman, J. C.; Lewis, L. N.; Caulton, K. G. *Inorg. Chem.* **1980**, *19*, 2755). All atoms, including hydrogens, were located and refined to final residuals $R(F)$ = 0.0560 and $R_w(F)$ = 0.0536. For tables of final parameters and observed and calculated structure factors, see: Langs, D.; Huffman, J. C. Report No. 82055, Molecular Structure Center, Indiana University.

(46) (*S*)-2-Methylbutyric anhydride was prepared according to the procedure outlined in ref 13.



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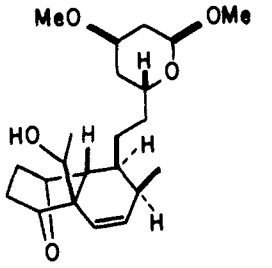

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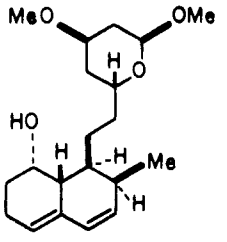

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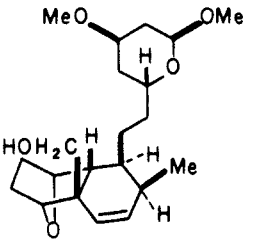
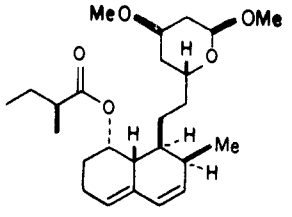


95

triethylamine in methylene chloride containing a catalytic amount of 4-(dimethylamino)pyridine, thus giving rise to ester **96** in 97% yield. Hydrolysis of the mixed acetal followed by oxidation of the resulting lactol with Fetizon's reagent[47] provided lactone **97** in 75% yield.



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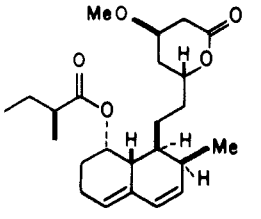

97

The demethylation of **97** proved to be exceedingly troublesome. Eager to confirm the structure of **97**, we cooled an ethereal solution of natural compactin[48] in ether containing silicAR CC-7 to 0 °C and treated it with gaseous diazomethane.[49] An 85% yield of **97** was obtained which was identical in all respects (melting point, NMR, IR, $[\alpha]_D$, TLC, and HPLC) with the synthetic sample of **97** prepared above.

When we were assured that the structure of **97** was correct, the problem of demethylating **97** resurfaced. Attempted demethylation with phenyl trimethylsilyl disulfide according to the procedure of Hanessian[50] led to the production of complex mixtures. Similar results were obtained with trimethylsilyl iodide and pyridine in methylene chloride[51] or with trimethylsilyl iodide generated in situ.[52] Also unsuccessful was boron trifluoride etherate in ethanedithiol.[53] Demethylation was finally accomplished by using boron tribromide in methylene chloride at −23 °C. Compactin was isolated in 31% yield. The physical and spectral properties of synthetic compactin were identical with those of a sample of natural compactin.

Experimental Section[54]

Methyl 2,4-Dideoxy-6-*O*-trityl-α-D-*erythro*-hexopyranoside (72). To a stirred solution of epoxide **7**[17] (19.9 g, 49.5 mmol) in 660 mL of anhydrous ether at −10 °C under argon was added lithium aluminum hydride (3.76 g, 99.0 mmol) in one portion. After 3.5 h at −10 °C the reaction was quenched by the dropwise addition of water (10.8 mL). The reaction mixture was filtered through a pad of anhydrous magnesium sulfate and washed thoroughly with ether. Concentration under reduced pressure afforded 19.7 g (98%) of alcohols **72** and **73** as an 11:1 mixture, respectively, of white crystals. Recrystallization from ether–hexane afforded alcohol **72** exclusively: mp 103.0–103.5 °C; R_f 0.41 (ether–hexane, 1:1); $[\alpha]_D$ +46.7° (*c* 1.63, $CHCl_3$). Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.30; H, 7.08.

Methyl 2,4-Dideoxy-3-*O*-methyl-6-*O*-trityl-α-D-*erythro*-hexopyranoside (74). Sodium hydride (15.8 g, 0.375 mol, 56.8% oil dispersion) was added to a 2-L round-bottom flask under argon and washed with pentane (150 mL). Dry tetrahydrofuran (250 mL) was added, and the stirred suspension was heated to reflux. To this refluxing suspension was added dropwise via cannula the 11:1 mixture of alcohols **72** and **73** (50.5 g, 0.125 mol) in 500 mL of dry tetrahydrofuran. After 30 min the solution was cooled to room temperature, and methyl iodide (46.7 mL, 0.750 mol) was added dropwise via syringe. After stirring at room temperature for 18 h the solution was cooled to 0 °C, the reaction quenched by the dropwise addition of water (5 mL), and the mixture filtered through Celite and washed with ether (500 mL). The filtrate was concentrated at reduced pressure and the residue taken up in ether (500 mL) and washed with water (100 mL). Drying ($MgSO_4$), filtering, and concentrating in vacuo left ca. 50 g of a mixture of methyl ethers **74** and **75** as a yellow oil. Separation of methyl ethers **74** and **75** was accomplished on a Waters Prep LC/System 500A, using two Prep-PAK-500/silica cartridges (57 mm × 30 cm, ethyl acetate–hexane, 13:87, flow rate 300 mL/min, two 25-g injections). The retention times of methyl ethers **75** and **74** were 6.9 and 11.0 min, respectively. The less polar methyl ether **75** [4.23 g (8%)] crystallized from ether–hexane: mp 101–102.5 °C; R_f 0.75 (ether–hexane, 1:1).

The more polar methyl ether **74** (46.1 g) was obtained in 88% yield as a syrup: R_f 0.57 (ether–hexane, 1:1); $[\alpha]_D$ +42.7° (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found C, 76.92; H, 7.38.

Methyl 2,4-Dideoxy-3-*O*-methyl-α-D-*erythro*-hexopyranoside (76). A solution of 4.32 g (0.188 mol) of sodium in ca. 1.7 L of anhydrous ammonia (dried by prior distillation from sodium) under argon was cooled to −78 °C. Trityl ether **74** (20.1 g, 0.048 mol) in 150 mL of dry tetrahydrofuran was added via cannula. The solution was stirred at −78 °C for 30 min and at reflux for 30 min prior to addition of 5 g of solid ammonium chloride. The ammonia was evaporated, and the residue was taken up in 150 mL of ethyl acetate and 200 mL of water. The aqueous layer was saturated by the addition of solid sodium chloride, and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 150 mL), and the combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product (ca. 20 g) was chromatographed on 200 g of silica gel. Elution with ether afforded 6.71 g (79%) of alcohol **76** as a colorless oil: R_f 0.25 (ether); $[\alpha]_D$ +132.1° (*c* 1.24, $CHCl_3$). Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.44; H, 9.11.

Methyl 2,4-Dideoxy-3-*O*-methyl-α-D-*erythro*-hexopyranoside, *p*-Toluenesulfonate. To a stirred solution of alcohol **76** (4.2 g, 23.9 mmol) in 25 mL of dry pyridine was added 4.78 g (25.1 mmol) of *p*-toluenesulfonyl chloride at 0 °C under argon. After 15 min the solution was warmed to room temperature and stirred for 11 h. The precipitate was filtered and was washed with 100 mL of ether. The filtrate was extracted with a solution of saturated aqueous copper sulfate (2 × 50 mL), saturated aqueous sodium bicarbonate solution (25 mL), and water (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue of ca. 8 g was chromatographed on 100 g of silica gel. Elution with hexane–ether (1:1) gave 7.53 g (96%) of tosylate as a colorless oil which was used directly in the next reaction: R_f 0.29 (ether–hexane, 2:1); $[\alpha]_D$ +61.4° (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71. Found: C, 54.99; H, 6.96.

(2*S*,4*R*,6*S*)-Tetrahydro-2-(iodomethyl)-4,6-dimethoxy-2*H*-pyran (77). To a stirred solution of the above tosylate (4.50 g, 13.6 mmol) in

(47) Fetizon, M.; Golfier, M. *C. R. Seances Acad. Sci., Ser. C* **1968**, *267*, 900.

(48) We are indebted to Prof. E. H. Goh (Department of Pharmacology, Indiana University) for a generous gift of natural compactin (**1**).

(49) Cf.: Ohno, K.; Nishiyama, M.; Nagase, H. *Tetrahedron Lett.* **1979**, 4405.

(50) Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* **1980**, 2305.

(51) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(52) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(53) Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2237.

(54) At the request of the editor, spectral data have been incorporated in the supplementary material.

40 mL of 2-butanone was added 5.11 g (34.1 mmol) of sodium iodide at room temperature under argon. The solution was heated to reflux in the dark for 4 h. After cooling to room temperature the solution was concentrated in vacuo, and 50 mL of water was added. The solution was extracted with ether (3 × 100 mL). The ethereal extracts were combined and washed with a saturated solution of sodium thiosulfate (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo leaving ca. 4 g of crude product which was purified on 80 g of silica gel. Elution with hexane–ether (65:35) afforded 3.75 g (96%) of iodide **77** as a colorless oil: R_f 0.65 (ether–hexane, 2:1); $[\alpha]_D$ +82.1° (*c* 2.42, $CHCl_3$).

Methyl 7ξ-Methyl-2,4,6,7-tetradeoxy-3-*O*-methyl-7-(phenylsulfonyl)-α-D-*erythro*-octopyranoside, Uronate (80). Sodium hydride (532 mg, 12.6 mmol, 56.8% oil dispersion) was added to a dry 100-mL round-bottom flask under argon and washed with pentane (25 mL). Dry dimethyl sulfoxide (30 mL) was added via syringe, and the solution was stirred at ca. 80 °C for 1.5 h. To this stirred solution was added solid methyl (phenylsulfonyl)acetate (2.89 g, 13.5 mmol) in one portion. After 15 min, iodide **77** (1.29 g, 4.50 mmol) in 6 mL of dry dimethyl sulfoxide was added via syringe in one portion. After stirring for 9 h at ca. 80 °C the solution was cooled to room temperature, and 200 mL of water was added, followed by solid sodium chloride until the solution was saturated. The ethereal extracts (4 × 200 mL) were dried ($MgSO_4$), filtered, and concentrated in vacuo, leaving ca. 4 g of crude product which was purified on 40 g of silica gel. Elution with hexane–ether (1:3) gave 1.51 g (90%) of sulfone **80** as a 2:1 mixture of diastereomers (NMR analysis). Crystallization took place upon cooling, and recrystallization from ether–hexane afforded colorless prisms of the major diastereomer: mp 103–105 °C; R_f 0.28 (ether–hexane, 3:1); $[\alpha]_D$ +27.7° (*c* 0.90, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_7S$: C, 54.83; H, 6.49; S, 8.61. Found: C, 54.88; H, 6.37; S, 9.05.

Methyl (2*R*,4*R*,6*S*)-Tetrahydro-4,6-dimethoxy-2*H*-pyran-2-propionate (79, R = CH_3). To a stirred solution of sulfone **80** (96 mg, 0.26 mmol) in 3 mL of anhydrous methanol at 0 °C under argon was added sodium phosphate dibasic (147 mg, 1.03 mmol) followed by pulverized 6% sodium amalgam (400 mg). After 15 min the solution was filtered and treated with 25 mL of ether and 25 mL of brine. The product was isolated by extraction with ether (3 × 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure, leaving ca. 100 mg of crude product which was purified by chromatography using 3 g of silica gel. Elution with ether–hexane (2:3) afforded 55 mg (92%) of ester **79** (R = CH_3) as a colorless oil: R_f 0.58 (ether–hexane, 3:1); $[\alpha]_D$ +110.6° (*c* 2.01, $CHCl_3$). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.58; H, 8.79.

(2*R*,4*R*,6*S*)-Tetrahydro-4,6-dimethoxy-2*H*-pyran-2-propanol (81). To a stirred solution of lithium aluminum hydride (77 mg, 2.04 mmol) in 15 mL of anhydrous ether at 0 °C under argon was added, dropwise via syringe, 473 mg (2.04 mmol) of ester **79** (R = CH_3) in 2 mL of anhydrous ether. After the mixture stirred for 15 min the reaction was quenched by the dropwise addition of water (100 μL). The solution was filtered through anhydrous magnesium sulfate, and the aluminum salts were washed with ether. Concentration of the filtrate left 416 mg (100%) of alcohol **81** as a colorless oil: R_f 0.18 (ether–hexane, 3:1); $[\alpha]_D$ +117.3° (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.75; H, 9.72.

(2*R*,4*R*,6*S*)-Tetrahydro-4,6-dimethoxy-2*H*-pyran-2-propionaldehyde (82). Dry pyridine (24.0 mL, 298 mmol) and 500 mL of dry methylene chloride were added to a dry 1-L three-neck flask equipped with a mechanical stirrer under argon. The solution was cooled to 0 °C, and 14.9 g (149 mmol) of dry chromium trioxide was added. After 20 min at 0 °C dry Celite (75 g) was added followed by the addition of 2.0 g (10.0 mmol) of alcohol **81** in 10 mL of dry methylene chloride. After 20 min the mixture was diluted with 300 mL of ether, was filtered through Celite (150 g), and was washed thoroughly with ether (1.5 L). Concentration under reduced pressure afforded crude aldehyde (3 g) which was purified on 50 g of silicAR CC-7. Elution with ether–hexane (3:1) afforded 1.81 g (90%) of aldehyde **82** as a slightly yellow sensitive material: R_f 0.51 (ether); $[\alpha]_D$ +126.0° (*c* 2.14, $CHCl_3$).

(*E*)-(2*R*,4*R*,6*S*)-Trimethyl[6-(tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)-3-hexen-1-ynyl]silane (83). To a stirred slurry of 718 mg (1.58 mmol) of ((trimethylsilyl)propargylidene)triphenylphosphonium bromide in 6 mL of dry tetrahydrofuran cooled to −78 °C under argon was added, dropwise via syringe, 937 μL of a 1.69 M solution of *n*-butyllithium in hexane. The resulting red solution was stirred at −45 °C for 30 min and was cooled to −78 °C. Aldehyde **82** (213 mg, 1.06 mmol) in 1.0 mL of dry tetrahydrofuran was added dropwise via syringe. The solution was allowed to warm to room temperature. After 1 h the crude reaction mixture was chromatographed on 15 g of silica gel. Elution with ether–hexane (3:7) afforded 256 mg (82%) of trimethylsilyl enyne **83** as a 9(*E*):1(*Z*) mixture of isomers: R_f 0.59 (ether–hexane, 1:2); $[\alpha]_D$ +84.3° (*c* 1.90, $CHCl_3$).

(*E*)-(2*R*,4*R*,6*S*)-2-(3-Hexen-5-ynyl)tetrahydro-4,6-dimethoxy-2*H*-pyran (84). To a stirred solution of 28 mg (0.095 mmol) of trimethylsilyl enyne **83** in 1.5 mL of dry tetrahydrofuran at 0 °C under argon was added, dropwise via syringe, 114 μL of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran. After stirring for 10 min the solution was concentrated in vacuo. To the residue was added 26 mL of ether and 10 mL of water. The layers were separated. The aqueous layer was extracted with 26 mL of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, and filtered. Concentration under reduced pressure provided ca. 25 mg of a yellow oil which was purified on 1 g of silica gel. Elution with ether–hexane (1:4) afforded 23 mg (100%) of enyne **84** as a 9(*E*):1(*Z*) mixture of double-bond isomers: R_f 0.55 (ether–hexane, 1:2); $[\alpha]_D$ +115.0° (*c* 1.90, $CHCl_3$).

(3*E*)-(2*S*,4*R*,6*R*)-Tetrahydro-2,4-dimethoxy-6-[6-(phenylthio)-3,5-hexadienyl]-2*H*-pyran (62). To a stirred solution of 512 mg (2.28 mmol) of enyne **84** in 2.0 mL of dry hexamethylphosphoramide at room temperature under argon was added 258 μL (2.51 mmol) of thiophenol and a catalytic amount of 2,2′-dimethyl-2,2′-azopropionitrile. The solution was submerged into a preheated oil bath set at ca. 150 °C for 5 min. The solution was cooled to room temperature and purified by chromatography on 40 g of silicAR CC-7. Elution with ether–hexane (1:4) afforded 714 mg (94%) of diene **62** as a 3(*E*):2(*Z*) mixture about the vinyl sulfur carbon–carbon bond: R_f 0.43 (ether–hexane, 1:1).

Methyl (1*R*,2*S*,3*S*,4*S*)-3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylate (69). To a solution of 5.02 g (26.9 mmol) of racemic acid **66**[15] and 3.69 g (26.9 mmol) of D-(−)-phenylglycinol in 90 mL of dry methylene chloride at 0 °C was added via cannula 6.66 g (32.3 mmol) of dicyclohexylcarbodiimide in 60 mL of dry methylene chloride. After stirring for 10 min at 0 °C the reaction mixture was warmed to room temperature and stirred for 1.75 h. The reaction mixture was filtered and the filtrate washed with 50 mL of saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Separation of amides **67** and **68** was accomplished on a Waters Prep LC/System 500A using two Prep-PAK-500/silica cartridges (57 mm × 30 cm, ethyl acetate–hexane, 7:3, flow rate 300 mL/min). The retention times of **67** and **68** were 4.5 and 11.5 min, respectively. The less polar amide **67** (3.59 g, 86% from acid **66**) was immediately dissolved in 33 mL of absolute methanol and treated with 33 mL of a 6 M solution of hydrogen chloride in absolute methanol. The solution was stirred at reflux for 3 h, then cooled to room temperature, and concentrated in vacuo. The residue was dissolved in water (25 mL) and extracted with ether (4 × 30 mL). The ethereal extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on 100 g of silica gel. Elution with ether–pentane (3:7) afforded 1.26 g (48% from **66**) of optically pure ester **69** as a slightly yellow oil: R_f 0.73 (ethyl acetate–hexane, 1:1); $[\alpha]_D$ −82.6° (*c* 3.05, $CHCl_3$). Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.50; H, 5.51; N, 6.86.

The more polar diastereomer **68** gave rise to 1.26 g (48% from **66**) of methyl ester **70**: $[\alpha]_D$ +78.49° (*c* 3.78, $CHCl_3$).

Methyl (1*R*,4*S*)-7-Oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (23). To a solution of 1.23 g (6.12 mmol) of ester **69** in 10 mL of methylene chloride was added 2.1 mL (14.1 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene, and the solution was refluxed for 2 h. After cooling to room temperature the reaction mixture was chromatographed on 100 g of silica gel. Elution with ether–pentane (3:7) afforded 700 mg (75%) of unsaturated ester **23** as a clear oil: R_f 0.53 (ether–hexane, 1:1); $[\alpha]_D$ +179.3° (*c* 1.88, $CHCl_3$). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.17; H, 6.40.

Methyl (1*S*,4*R*,4a*S*,5*R*,8*S*,8a*R*)-1,3,4,5,8,8a-Hexahydro-5-(phenylthio)-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)-ethyl]-1,4-epoxynaphthalene-4a(2*H*)-carboxylate (85). A solution of 520.0 mg (1.56 mmol) of diene **62**, 80.0 mg (0.52 mmol) of dienophile **23**, and 46.0 mg (0.21 mmol) of 2,6-di-*tert*-butyl-4-methylphenol in 2.5 mL of degassed dry toluene was heated at 125 °C, in the absence of light, in a sealed tube (washed with potassium hydroxide–ethanol). After 14 h, the reaction mixture was cooled to room temperature and directly chromatographed on 20 g of silica gel (gradient elution with ether–hexane, 3:7–2:3) to afford 217 mg (86%) of sulfides **85** and **86** (7:3 mixture, respectively) as a yellow oil. Separation of the two regioisomers on a Waters Analytical HPLC system, using a μ-Porasil (P/N 84175 S/N) column 7.8 mm × 30 cm, ethyl acetate–hexane, 1:4, flow rate 6 mL/min), afforded adduct **85** (retention time 12.3 min): R_f 0.16 (ether–hexane, 1:1); $[\alpha]_D$ +61.5° (*c* 1.35, $CHCl_3$). Anal. Calcd for $C_{27}H_{36}O_6S$: C, 66.38; H, 7.43. Found: C, 66.71; H, 7.87. Continued elution afforded pure adduct **86** (retention time 14.5 min).

Methyl (1*S*,4*R*,4a*R*,7*S*,8*R*,8a*R*)-1,3,4,7,8,8a-Hexahydro-7-hydroxy-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)-

ethyl]-1,4-epoxynaphthalene-4a(2*H*)-carboxylate (87). To a solution of 268 mg (0.754 mmol) of sulfides **85** and **86** (7:3 mixture, respectively) in 20 mL of dry methylene chloride at −78 °C under argon was added dropwise a solution of 169 mg (0.98 mmol) of *m*-chloroperbenzoic acid in 15 mL of dry methylene chloride. After 2 h at −78 °C, the excess oxidant was destroyed by the addition of 500 μL of dimethyl sulfide. After an additional 30 min at −78 °C, the reaction mixture was warmed to room temperature and diluted with 50 mL of methylene chloride. The reaction mixture was washed with 25 mL of a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on 30 g of neutral silica gel (elution with ether) afforded 232 mg of crude allylic sulfenate which was directly dissolved in 2.5 mL of dry methanol. To the above solution was added 270 μL (2.3 mmol) of trimethyl phosphite, and the reaction mixture was stirred at reflux for 2.5 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The product was chromatographed on 12 g of silica gel. Elution with ethyl acetate–hexane (3:27) afforded 178 mg (60%) of the desired allylic alcohol **87** as a colorless oil: R_f 0.27 (ether); $[\alpha]_D$ +36.7° (*c* 2.55, $CHCl_3$).

Methyl (1*S*,4*R*,4a*R*,7*R*,8*R*,8a*R*)-1,3,4,7,8,8a-Hexahydro-7-benzoxy-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)-ethyl]-1,4-epoxynaphthalene-4a(2*H*)-carboxylate (90, R = COPh). To a solution of 43.0 mg (0.11 mmol) of alcohol **87**, 26.6 mg (0.218 mmol) of benzoic acid (freshly sublimed), and 57.0 mg (0.22 mmol) of triphenylphosphine, recrystallized from ether, in 1 mL of dry tetrahydrofuran at room temperature under argon was added dropwise a solution of 38.0 mg (0.22 mmol) of diethyl azodicarboxylate in 250 μL of dry tetrahydrofuran. After 15 min at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in 40 mL of methylene chloride, washed with 10 mL of a 5% sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography of the residue on 17 g of silica gel (elution with ether–hexane, 1:1) afforded 50.9 mg (93%) of allylic benzoate **90** (R = COPh) as a colorless oil: R_f 0.37 (ethyl acetate–hexane, 3:1); $[\alpha]_D$ −98.9° (*c* 1.48, $CHCl_3$). Anal. Calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25. Found: C, 67.12; H, 7.20.

Methyl (1*S*,4*R*,4a*R*,7*R*,8*R*,8a*R*)-1,3,4,7,8,8a-Hexahydro-7-hydroxy-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)-ethyl]-1,4-epoxynaphthalene-4a(2*H*)-carboxylate (90, R = H). To a stirred solution of 137.0 mg (0.26 mmol) of benzoate **90** (R = COPh) in 500 μL of dry methanol under argon was added 3 mL of a 1.9 M solution of sodium methoxide in methanol. After 2.5 h at room temperature, the solvent was removed in vacuo. The residue was dissolved in 80 mL of ether, was washed with 20 mL of a 5% hydrochloric acid solution, was dried over anhydrous magnesium sulfate, and was concentrated in vacuo. Chromatography on 8 g of silica gel (elution with ether) afforded 88 mg (85%) of alcohol **90** (R = H) as a crystalline material. Recrystallization from ether afforded pure alcohol **90** (R = H): mp 124.0–125.0 °C; R_f 0.28 (ether); $[\alpha]_D$ −40.8° (*c* 1.61, $CHCl_3$).

Methyl (1*S*,4*R*,4a*R*,7*R*,8*R*,8a*R*)-1,3,4,7,8,8a-Hexahydro-7-acetoxy-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)-ethyl]-1,4-epoxynaphthalene-4a(2*H*)-carboxylate (90, R = Ac). To a stirred solution of 75.3 mg (0.190 mmol) of alcohol **90** (R = H), 48 μL (0.34 mmol) of dry triethylamine, and 2 mg of 4-(dimethylamino)-pyridine in 3 mL of dry methylene chloride was added 32 μL (0.34 mmol) of acetic anhydride. The reaction mixture was allowed to stir overnight. The reaction mixture was diluted with 20 mL of ether and was washed with 15 mL of a 5% sodium bicarbonate solution. The aqueous phase was extracted with ether (2 × 10 mL). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on 15 g of silica gel (elution with ether–hexane, 1:1) afforded 83 mg (100%) of acetate **90** (R = Ac) as a colorless oil: R_f 0.56 (ether); $[\alpha]_D$ −63.1° (*c* 1.34, $CHCl_3$). Anal. Calcd for $C_{23}H_{34}O_8$: C, 63.00; H, 7.82. Found: C, 63.13; H, 8.11.

Methyl (1*S*,4*R*,4a*R*,7*S*,8*S*,8a*R*)-1,3,4,7,8,8a-Hexahydro-7-methyl-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)ethyl]-1,4-epoxynaphthalene-4a(2*H*)-carboxylate (91). To a suspension of 410 mg (2.16 mmol) of cuprous iodide in 10 mL of dry ether at 0 °C under argon was added dropwise 2.78 mL (4.32 mmol) of a 1.55 M solution of methyllithium in ether. The resulting cloudy white solution was stirred for 5 min at 0 °C and cooled to −10 °C upon which a solution of 63.0 mg (0.144 mmol) of acetate **90** (R = Ac) in 4 mL of dry ether was added via cannula. The resulting yellow suspension was stirred at −10 °C for 1 h, followed by being warmed to room temperature. The reaction was quenched by the addition of 15 mL of a saturated ammonium chloride solution. The aqueous phase was extracted with ether (3 × 20 mL). The combined extracts were washed with 15 mL of a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography of the residue on 8 g of silica gel (elution with ether–hexane, 1:1) afforded 49.0 mg (86%) of **91** as a clear oil: R_f 0.64 (ether–hexane, 3:1); $[\alpha]_D$ +59.1° (*c* 1.56, $CHCl_3$).

(1*S*,4*R*,4a*S*,7*S*,8*S*,8a*R*)-1,3,4,7,8,8a-Hexahydro-7-methyl-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)ethyl]-1,4-epoxynaphthalene-4a(2*H*)-methanol (95). To a solution of 80.0 mg (0.20 mmol) of ester **91** in 8 mL of dry ether at 0 °C under argon was added 31 mg (0.81 mmol) of lithium aluminum hydride in one portion. After 2 h at 0 °C the reaction was quenched by dropwise addition of 200 μL of water. The reaction mixture was filtered through a pad of anhydrous magnesium sulfate and was concentrated in vacuo, leaving 73.0 mg (98%) of alcohol **95** as a clear oil: R_f 0.34 (ether); $[\alpha]_D$ +87.9° (*c* 2.03, $CHCl_3$).

(1*S*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)ethyl]-1-naphthol (94). To a suspension of 40 mg (1.0 mmol) of potassium hydride prewashed with pentane in 500 μL of dry toluene under argon was added via cannula a solution of 24.3 g (0.67 mmol) of alcohol **95** in 2 mL of dry toluene. After 5 min at room temperature, the reaction mixture was submerged into a preheated bath at 120 °C. After 3 h at reflux, the reaction mixture was cooled to 0 °C, and the reaction was quenched by the addition of 10 mL of a saturated ammonium chloride solution. The aqueous phase was extracted with ether (5 × 10 mL). The combined extracts were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed in vacuo. Chromatography of the residue on 6 g of silica gel (elution with ether–pentane, 1:1) afforded 8.8 mg (40%) of diene **94** as a colorless oil: R_f 0.38 (ether–hexane, 4:1); $[\alpha]_D$ +219.2° (*c* 1.20, $CHCl_3$).

(1*S*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-[2-((2*R*,4*R*,6*S*)-tetrahydro-4,6-dimethoxy-2*H*-pyran-2-yl)ethyl]-1-naphthyl (2*S*)-2-Methylbutyrate (96). To a solution of 7.0 mg (0.021 mmol) of alcohol **94**, 12 μL (0.084 mmol) of dry triethylamine, and 3.8 mg (0.031 mmol) of 4-(dimethylamino)pyridine in 400 μL of dry methylene chloride was added 14 μL (0.063 mmol) of (*S*)-2-methylbutyric anhydride.[46] After 16 h at room temperature, the reaction mixture was directly chromatographed on 3 g of silica gel. Elution with ether–pentane (2:3) afforded 8.4 mg (97%) of ester **96** as a colorless oil: R_f 0.45 (ether–hexane, 1:1); $[\alpha]_D$ +247.7° (*c* 1.48, $CHCl_3$). Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.77; H, 9.67. Found: C, 68.05; H, 9.43.

(1*S*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-[2-((2*R*,4*R*)-tetrahydro-4-methoxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthyl (2*S*)-2-Methylbutyrate (97). To a solution of 13.2 mg (0.0314 mmol) of methoxy hemiacetal **96** in 500 μL of tetrahydrofuran was added 300 μL of a 10% hydrochloric acid solution. After 20 min at 45 °C, the reaction mixture was cooled to room temperature and was concentrated in vacuo to half its original volume. The residue was dissolved in 50 mL of ether and was washed with 10 mL of a saturated sodium bicarbonate solution. The aqueous phase was extracted with 50 mL of ether. The combined extracts were dried over anhydrous magnesium sulfate and filtered. Concentration in vacuo afforded 13.8 mg of a mixture of lactols which were used directly in the next reaction.

To a solution of the above lactols in 3 mL of dry benzene was added 195 mg (0.314 mmol, 48% by weight on Celite) of silver carbonate. After 4 h at reflux in the absence of light the reaction mixture was cooled to room temperature and filtered through a pad of Celite, with thorough washing with ether. Concentration of the filtrate in vacuo and chromatography on 3 g of silica gel (elution with ether–hexane, 2:3) afforded 9.0 mg (71%) of lactone **97** as a crystalline material: mp 98.5–100.0 °C; R_f 0.37 (ether–hexane, 3:1); $[\alpha]_D$ +243.1° (*c* 1.14, $CHCl_3$). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.09; H, 8.86.

Methylation of Natural Compactin. To a solution of 92.0 mg (0.24 mmol) of compactin (**1**) in 15 mL of dry ether was added 5.5 g of silicAR CC-7 silica gel (oven dried, 120 °C). This suspension was stirred at 0 °C while gaseous diazomethane (generated from a heterogeneous mixture of 100 mL of a 40% potassium hydroxide solution, 10 mL of anisole, and ca. 300 mg of *N*-methyl-*N*-nitrosourea) was bubbled through the suspension using nitrogen as the carrier gas. Every 30 min ca. 300 mg of urea was added to the 40% potassium hydroxide/anisole mixture and the process repeated until ca. 1.2 g of the urea was used. The reaction mixture was filtered and washed with 200 mL of ether. The filtrate was concentrated in vacuo and the residue chromatographed on 20 g of silica gel. Elution with ether–hexane (3:1) afforded 35.9 mg (38%, 85% based on recovered **1**) of lactone **97**, which was identical in all respects with the sample of **97** prepared above. Continued elution afforded 51.7 mg (56%) of recovered compactin.

Compactin (1). To a solution of 40 mg (0.099 mmol) of methyl ether **97** in 750 μL of dry methylene chloride (distilled from phosphorous pentoxide) at −78 °C under argon was added, via syringe, boron tribromide (75 μL, 0.79 mmol). The reaction mixture was warmed to −23 °C and stirred for 5 h. The reaction was quenched by addition of dry ether (2 mL) followed by addition of the mixture, via cannula, to a stirred cooled (0 °C) solution of saturated aqueous sodium bicarbonate (15 mL). After 15 min, the layers were separated, and the aqueous layer was

extracted with ether (2 × 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, leaving 15 mg of residue which was purified by chromatography using 10 g of silicAR CC-7. Elution with ether–hexane (1:1) afforded 11.8 mg (31%) of compactin (**1**): mp 150–151 °C [lit.[1] mp 152 °C]; R_f 0.50 (ether); $[\alpha]_D$ +291.0° (*c* 0.205, acetone) [lit.[1] $[\alpha]_D^{22}$ + 283° (*c* 0.84, acetone)].

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Registry No. 1, 73573-88-3; **7**, 73541-95-4; **23**, 84751-39-3; (*E*)-**62**, 84800-51-1; (*Z*)-**62**, 84751-58-6; (±)-**66**, 84751-42-8; **67**, 84751-55-3; **68**, 84799-47-3; **69**, 84751-43-9; **70**, 103530-11-6; **72**, 86030-92-4; **73**, 91312-60-6; **74**, 103456-59-3; **75**, 103438-11-5; **76**, 84751-44-0; **77**, 84751-56-4; **79** (R = CH_3), 84751-45-1; **80** (isomer 1), 103438-13-7; **80** (isomer 2), 103438-14-8; **81**, 103438-15-9; **82**, 84751-57-5; (*E*)-**83**, 84751-46-2; (*Z*)-**83**, 103530-09-2; (*E*)-**84**, 103438-16-0; (*Z*)-**84**, 103530-10-5; **85**, 84751-40-6; **86**, 103438-17-1; **87**, 84751-47-3; **87** (sulfenate), 84751-59-7; **90** (R = H), 84799-48-4; **90** (R = Ac), 103438-18-2; **90** (R = COPh), 84751-48-4; **91**, 84751-49-5; **94**, 84751-51-9; **95**, 84751-50-8; **96**, 84751-52-0; **97**, 84751-53-1; **97** (lactol isomer 1), 103438-19-3; **97** (lactol isomer 2), 103530-60-5; methyl 2,4-dideoxy-3-*O*-methyl-α-D-*erythro*-hexopyranoside, *p*-toluenesulfonate, 103438-12-6; ((trimethylsilyl)propargylidene)triphenylphosphonium bromide, 42134-49-6; 2,2′-dimethyl-2,2′-azopropionitrile, 78-67-1; D-(−)-phenylglycinol, 56613-80-0; 1,8-diazabicyclo[5.4.0]undec-7-ene, 6674-22-2; 2,6-di-*tert*-butyl-4-methylphenol, 128-37-0; (*S*)-2-methylbutyric anhydride, 84131-91-9.

Supplementary Material Available: Experimental details and spectral and analytical data for **25**, **31**, **32**, **34–36**, **38**, **40**, **43**, **44**, **46–50**, **55**, and **56** and spectral data for **1**, **23**, **62**, **69**, **72**, **74–77**, **79–87**, **90**, **91**, and **94–97** (22 pages). Ordering information is given on any current masthead page.

Chiral Synthesis via Organoboranes. 7. Diastereoselective and Enantioselective Synthesis of *erythro*- and *threo*-β-Methylhomoallyl Alcohols via Enantiomeric (*Z*)- and (*E*)-Crotylboranes

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Abstract: Isomerically pure (*Z*)- and (*E*)-crotylpotassiums have been prepared by metalation of (*Z*)- and (*E*)-2-butene using a modified Schlosser procedure. The enantiomerically pure (*Z*)-crotyldiisopinocampheylboranes **16A** and **16B** have been prepared by employing methoxydiisopinocampheylboranes [**20A** or **20B**, prepared from either (+)- or (−)-α-pinene] and (*Z*)-crotylpotassium (**19**), prepared as indicated above. These enantiomeric (*Z*)-crotylboranes, **16A** and **16B**, the first such derivatives to be synthesized, retain their stereochemical identity under the reaction conditions and have been successfully condensed with various aldehydes, such as acetaldehyde, propionaldehyde, acrolein, and benzaldehyde, in a regioselective and stereoselective manner to yield the corresponding *erythro*-β-methylhomoallyl alcohols in ≥99% diastereoselectivities and ≥95% enantioselectivities. Similarly, the enantiomeric (*E*)-crotyldiisopinocampheylboranes **17A** and **17B** have been prepared from **20A** or **20B** and the pure (*E*)-crotylpotassium (**23**) derived from (*E*)-2-butene. Again, these boranes, **17A** and **17B**, add to representative aldehydes such as acetaldehyde, propionaldehyde, acrolein, and benzaldehyde in a similar fashion to yield the corresponding *threo*-β-methylhomoallyl alcohols in ≥99% diastereoselectivities and 95% enantioselectivities. Further, (*Z*)- and (*E*)-crotyldiisocaranylboranes (**16C** and **17C**) have been prepared and condensed with propionaldehyde to furnish the *erythro*- and *threo*-β-methylhomoallyl alcohols **8B** and **11B**, respectively, in ≥99% diastereoselectivities and improved enantioselectivities (97%).

β-Methylalkanol units of both erythro and threo configurations[2–4] are a characteristic structural element of numerous macrolide and polyether antibiotics.[5] This has aroused interest in the development of new synthetic methods which allow the stereoselective synthesis of β-methylalkanols. Even today there are conspicuous gaps in the registry of organic synthetic methods. Special attention has been given to those reactions in which new carbon–carbon bonds are formed via aldol addition, which constituted one of the fundamental bond constructions in biosynthesis[6,7] (eq 1 and 2). Hence, there has been a renewed interest in the development of stereoregulated aldol and related condensation reactions. Among such condensations are the reactions of allylic organometallic reagents with aldehydes, affording the

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(2) The terms erythro and threo are used in the sense defined by Heathcock.[3] This terminology is used by most of the groups working on aldol-type additions. It should be made clear that this usage is contrary to the rules defined by *Chemical Abstracts* or *Beilstein*.[4]

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