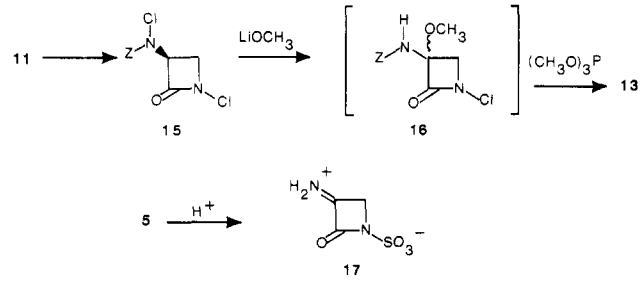
For implementation of Scheme II, a chemoselective sulfonation of the azetidinone nitrogen of **11** or **13** in the presence of the urethane nitrogen was needed. Despite the lack of literature precedent, we believed that the azetidinone nitrogen would be more nucleophilic because of reduced amide resonance.[13] Three sulfonation procedures (detailed in Scheme III) for the conversion of **11** to various salts of **12** have been developed. Reaction of **11** with 1 equiv of pyridine-sulfur trioxide complex[14,15] gave pyridinium salt **12a** in virtually quantitative yield. Chemoselective silylation of **11** also occurs on the azetidinone nitrogen; subsequent reaction[16] with trimethylsilyl chlorosulfonate gives the trimethylsilyl ester of **12** which is hydrolyzed in buffer to potassium salt **12b** (mp 193–196 °C,[6] isolated by HP-20 chromatography.[17] The most general procedure we have developed involves sulfonation with DMF–SO_3 complex[18] followed by quenching into buffer and ion-pair extraction to give directly tetra-*n*-butylammonium salt **12c** (mp 107–114.5 °C).[6]

Hydrogenolysis of **12c** in DMF gives **4**[19] in excellent yield. It is convenient to acylate **4** in situ by addition of equivalent amounts of RCO_2H, DCC, and *N*-hydroxybenzotriazole to the filtered hydrogenolysis mixture. Suitable workup gives good to excellent yields of **1** (X = H).

Conversion of **11** to **13** could be accomplished via the novel *N,N'*-dichloro derivative **15**.[20] We expected that the *N*-chloroazetidinone moiety would be inert to base treatment since it should be stable to endocyclic acylimine formation (increased ring strain) and to ring-opening elimination (stereoelectronic factors).[21] Subsequent removal of the *N*-chloroazetidinone "protecting group" by reduction was anticipated. The reaction of **15** with 1.1 equiv of lithium methoxide,[22] followed by reduction of **16** with trimethyl phosphite, gave racemic methoxyazetidinone **13** (44%, mp 112–114 °C).[6]

Sulfonation of **13** proved to be much slower compared to **11** due to electron withdrawal by the methoxy group but proceeded in high yield with excess pyridine–sulfur trioxide to give **14** after ion-pair extraction (mp 196–198 °C as the potassium salt[6]). Hydrogenolysis of **14** in acetonitrile or



methanol in the presence of 10 mol % sodium borate gave **5**[23] in high yield. When sodium borate was omitted the crude product showed virtually no CH_3O resonance (^1H NMR), suggesting acid-catalyzed decomposition via zwitterion **17** had intervened. Exchange of ethoxy for methoxy when the hydrogenolysis was performed in ethanol supports the formation of **17**. Acylation of **5** could be accomplished with acid chlorides to give racemic monobactams **1** (X = CH_3O). When acylating agents derived from enantiomerically-pure α-amino acids were utilized, the resulting mixture of diastereomeric monobactams could be separated[17] to provide biologically active 3*R* enantiomers of **1** (X = CH_3O).

The availability of **4** and **5** from 6-APA, and their ready conversion to monobactams (**1**), has enabled us to evaluate structure–activity relationships in this novel family of β-lactam antibiotics. The sulfonation–deprotection–acylation methodology reported in this communication has proved to be quite general. We will report its application to 4-substituted monobactams, including the synthesis of the first monobactam for clinical development (SQ 26,776, azthreonam[3]) in due course. In the accompanying communication,[24] we describe a conceptually different preparation of monobactams.

Registry No. 3, 551-16-6; **4**, 80082-73-1; (±)-**5**, 80082-75-3; **6**, 80082-77-5; **9**, 80082-79-7; **10**, 80082-80-0; **11**, 80082-81-1; **12a**, 80082-83-3; **12b**, 80082-84-4; **12c**, 80082-47-9; (±)-**13**, 78184-08-4; (±)-**14**, 80082-86-6; **15**, 80082-87-7; (±)-**16**, 80082-88-8.

(11) Bose, A. K.; Tasi, M.; Sharma, S. D.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1779–1783.
(12) Kamiya, T. In "Recent Advances in the Chemistry of β-Lactams"; Elks, J., Ed.; Special Publication No. 28, The Chemical Society; Burlington House: London, 1977; pp 281–294.
(13) Solution (CH_3CN) infrared spectra of **11** show carbonyl absorptions at 1773 (β-lactam) and 1725 cm^{-1} (urethane).
(14) Sulfonation of primary amides with pyridine–sulfur trioxide produces acylsulfamic acids ($RCONHSO_3H$): Baumgarten, P; Marggraff, I. *Chem. Ber.* **1931**, *64*, 1582–1588.
(15) A Takeda group has made extensive use of this reaction in the synthesis of monobactams including alternate salts of **12** and **14** and more than 100 other analogues. Single examples of hydrogenolysis–acylation of **12** and **14** are also reported (European Patent Applications 80 301 898.5 and 80 301 900.9, 1981).
(16) Acylation of N-silylated azetidinones has been reported: Kricheldorf, H. R. *Makromol. Chem.* **1973**, *170*, 89–103.
(17) HP-20 AG is the analytical grade of a macroreticular polystyrene–divinylbenzene copolymer available from Mitsubishi Chemical Industries, Ltd. We have made extensive use of chromatography of monobactam potassium salts on this medium.
(18) Prepared analogously to dioxane–sulfur trioxide: Hofman, K.; Simchen, G. *Synthesis* **1979**, 699–700.
(19) **4**: ^1H NMR ($CDCl_3$) 3.80 (apparent t, $J_{4\alpha-4\beta} \cong 6$ Hz, $J_{3\alpha-4\alpha} \cong 6$ Hz, 4α-H), 4.05 ppm (d of d, $J_{4\alpha-4\beta} \cong 6$ Hz, $J_{3\alpha-4\beta} \cong 3$ Hz, 4β-H).
(20) Prepared by dissolving **11** in methanol containing 4% sodium borate and adding 2.4 equiv of *tert*-butyl hypochlorite at 0 °C. After 30 min, extractive workup with ethyl acetate gave 98% of **15**.
(21) Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620–3622.
(22) This two-step chlorination–methoxylation sequence is a combination of the methods of Baldwin and Koppel: Baldwin, J. T.; Urban, F. J.; Cooper, R. D. G.; Jose, F. L. *J. Am. Chem. Soc.* **1973**, *95*, 2401–2403. Koppel, G. A.; Koehler, R. E. *J. Am. Chem. Soc.* **1973**, *95*, 2403–2404. The isolation of **15** under Baldwin's conditions suggests that an electron withdrawing moiety at C-4 of an azetidinone may be essential for C-3 proton removal in methanolic sodium borate solution.
(23) **5**: ^1H NMR (CD_3CN) 3.27 (CH_3O), 3.50 ppm (d, J = 6 Hz, C-4ABq - downfield part).
(24) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

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Hypocholesterolemic Agent Compactin (ML-236B). Total Synthesis of the Hexahydronaphthalene Portion

Summary: A synthesis of **2**, the hexahydronaphthalene portion of the hypocholesterolemic agent compactin (**1**), is described. The four contiguous asymmetric centers of **1** were established in an efficient stereospecific manner via a Lewis acid mediated intramolecular Diels–Alder reaction of **11**.

Sir: Compactin (or ML-236B, **1**), a fungal metabolite isolated virtually simultaneously in 1976 by Brown et al.[1]

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(Beecham Pharmaceuticals) from *Penicillium brevicompactum* and Endo et al.[2a] (Sankyo Co.) from *Penicillium citrinum*, is an extremely potent competitive inhibitor[2] of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme involved in the rate-limiting step of cholesterol biosynthesis.[3] In addition, compactin has been shown by the Sankyo group to substantially reduce plasma cholesterol levels in dogs, monkeys, and humans[4] and thus may prove to be a useful agent for treating diseases associated with high plasma cholesterol levels such as atherosclerosis and related coronary artery diseases. We describe herein a short, stereospecific synthesis of **2**, the structurally unique hexahydronaphthalene moiety[5] of compactin.

A retrosynthetic analysis of compactin suggests the coupling of an appropriately functionalized tetrahydropyran, ultimately derived from glucose, with a modified hexahydronaphthalene **2**, in turn available from the intramolecular Diels–Alder cycloadduct **3**. The intramolecular cycloaddition of dodecatrienoate **4** is expected to proceed through chairlike[6] endo[7] transition states A and B (rather than alternative exo modes), especially under the influence of Lewis acid catalysis.[8] Therefore, the three contiguous asymmetric centers in the cyclohexene ring of **3** should be introduced with the correct relative configuration analogous to those in compactin. The stereorelationship of the hydroxyl carbon center is certainly less predictable, although a possible $A^{1,3}$-type interaction[9] between the pseudoequatorial protected hydroxyl and the C-2 hydrogen might destabilize transition state B. Furthermore, in transition state A, the pseudoaxial protected hydroxyl is oriented for maximum hyperconjugative overlap ($\sigma^*_{C\text{-}O}$–π^*), perhaps leading to a transition-state-stabilizing effect (lowered LUMO for the unsaturated ester π system).

The synthesis of the dodecatrienoate **4** was relatively straightforward as outlined in Scheme I. Alkylation of

Scheme I

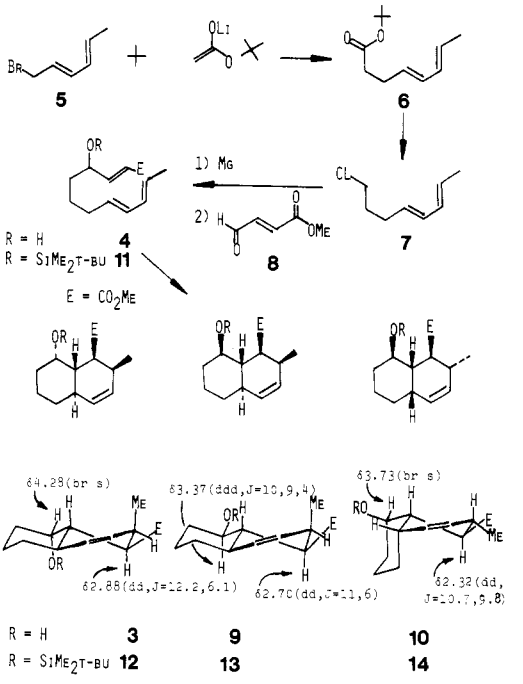


Table I. Intramolecular Diels–Alder Cycloaddition of Trienes 4 and 11

triene	conditions	yield, %	cycloadduct ratio, % 3	9	10
4 (R = H)	155 °C, 60 h	53	12	41	47
	25 °C, 23 h, 1 equiv of $EtAlCl_2$	55	55	45	1

triene	conditions	yield, %	cycloadduct ratio, % 12	13	14
11 (R = $SiMe_2$-*t*-Bu)	140 °C, 120 h	65	65	13	22
	25 °C, 72 h, 1 equiv of $EtAlCl_2$	65–73	98	2	0

(1) A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp, and R. H. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1165 (1976).

(2) (a) A. Endo, M. Kuroda, and K. Tanzawa, *FEBS Lett.*, **72**, 323 (1976); (b) A. Endo, M. Kuroda, and Y. Tsujita, *J. Antibiot.*, **29**, 1346 (1976); (c) A. Endo and K. Tanzawa, *Eur. J. Biochem.*, **98**, 195 (1979); (d) M. S. Brown, J. R. Faust, and J. L. Goldstein, *J. Biol. Chem.*, **253**, 1121 (1978).

(3) V. W. Rodwell, J. L. Nordstrom, and J. J. Mitschelen *Adv. Lipid Res.*, **14**, 1–74 (1976).

(4) (a) Y. Tsujita, M. Kuroda, K. Tanzawa, N. Kitano, and A. Endo, *Atherosclerosis (Shannon, Irel.)*, **32**, 307 (1978); (b) M. Kuroda, Y. Tsujita, K. Tanzawa, and A. Endo, *Lipids*, **14**, 585 (1979); (c) A. Yamamoto, H. Sudu, and A. Endo, *Atherosclerosis (Shannon, Irel.)*, **35**, 259 (1980).

(5) The isolation of a related member of this class of compounds, identical with compactin except for an α-methyl substituent at the secondary allylic position in the acyloxy-substituted ring, has recently been reported by two groups and named. (a) Mevinolin: A. W. Alberts, J. Chen, G. Kuron, V. Hunt, J. Huff, et al., *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 3957 (1980); (b) Monacolin K: A. Endo, *J. Antibiot.*, **32**, 852 (1979).

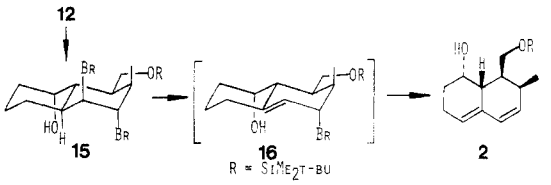
(6) Chairlike transition states have been invoked to explain the intramolecular Diels–Alder cycloadditions of various substituted 1,7,9-trienes when the four-carbon bridge is exo (as in this case). For example: (a) F. Naf, R. Decorzant, and W. Thommen, *Helv. Chim. Acta*, **62**, 114 (1979); (b) S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.*, **100**, 6289 (1978); (c) D. F. Taber and S. A. Saleh, *ibid.*, **102**, 5085 (1980); R. L. Funk and K. P. C. Vollhardt, *ibid.*, **102**, 5253 (1980). However, when an activating carbonyl forces the four-carbon bridge to add in the endo sense, then a boatlike transition state has been claimed. See: (d) D. F. Taber and B. P. Gunn, *ibid.*, **101**, 3992 (1979).

(7) When this work was initiated, relatively few intramolecular Diels–Alder reactions of terminally activated 2,8,10-trienoates had been studied. One such study has been undertaken wherein the majority of the Diels–Alder substrates cyclized preferentially through the ester exo mode to give rise to cis ring-fusion products. See: W. R. Roush and S. E. Hall, *J. Am. Chem. Soc.*, **103**, 5200 (1981). We thank Professor Roush for providing us with a manuscript prior to publication.

(8) (a) K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973). (b) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975). (c) For a dramatic illustration of this effect in the catalyzed reactions of decatrienoates producing perhydroindene cycloadducts, see: W. R. Roush and H. R. Gillis, *J. Org. Chem.*, **45**, 4267 (1980); W. R. Roush, A. I. Ko, and H. R. Gillis, *ibid.*, **45**, 4264 (1980).

(9) (a) F. Johnson, *Chem. Rev.*, **68**, 375 (1968). This type of steric interaction has been used to explain the stereochemical consequences of other intramolecular Diels–Alder reactions. For example: (b) K. C. Nicolaou and R. L. Magolda, *J. Org. Chem.*, **46**, 1506 (1981); (c) W. R. Roush and A. G. Myers, *ibid.*, **46**, 1509 (1981).

Scheme II



the lithium anion of *tert*-butyl acetate[10] with sorbyl bromide[11] (**5**) afforded the octadienoate **6** (81%).[12] Reduction of **6** with LAH gave (*E,E*)-octa-4,6-dien-1-ol in 86% yield which was then converted to the chloride **7** with $SOCl_2$ (71%). Treatment of the chloride **7** with Mg (1.2 equiv, THF) provided the corresponding Grignard reagent which was directly alkylated with oxobutenoate **8**[13] (−65 to −20 °C, THF) to afford, after chromatography, the Diels–Alder precursor **4** (51% yield, mp 41–42 °C).

When trienoate **4** was refluxed in degassed bromobenzene for 60 h, a mixture of three cycloadducts (**10**, **9**, and **3** in an HPLC ratio of ca. 47:41:12, respectively) was obtained after chromatography. The stereochemistry in the cyclohexenyl ring of each cycloadduct (Scheme I) was assigned upon analysis of the respective 360-MHz ^1H NMR spectrum. The experimental coupling patterns and chemical shifts are consistent with those expected for the assigned structures and are very similar to the analogous resonances of other intramolecular Diels–Alder cycloadducts derived from 2,8,10-trienoates.[7]

The relative amount of the desired cycloadduct **3** could be significantly increased (Table I) by the addition of $EtAlCl_2$, which presumably generates the alkoxyalane to provide a 55:45 ratio of **3**/**9** (55% combined yield) and only a trace of the exo adduct **10**. The *tert*-butyldimethylsilyl ether **11**, (from **4**, imidazole, $ClSiMe_2$-*t*-Bu, and DMF; 88%) gave the desired endo adduct **12** as the major product as well as the epimer **13** and some exo adduct **14** (65:13:22) upon being refluxed in degassed xylenes for 5 days (65% yield). Deprotection (HF, CH_3CN; 99%) provided an identical ratio of **3**/**9**/**10**. More significantly, under the influence of Lewis acid catalysis ($EtAlCl_2$, 3 days) the silyloxy trienoate **11** gave virtually exclusively (>98% one isomer) the endo adduct **12** (65–73%) accompanied by variable amounts (2–10%) of the deprotected cycloadduct **3**.

Various synthetic sequences for effecting formal dehydrogenation of octahydronaphthalene **3** have been investigated. The successful one is shown in Scheme II. Reduction (LAH) of ester **12** followed by hydrolysis gave a diol (HF, CH_3CN; 94% yield; mp 78–79 °C) which was selectively protected (1.2 equiv of $ClSiMe_2$-*t*-Bu, imidazole, DMF, 24 h; 80%) and brominated[14] (1 equiv of Br_2, 1 equiv of NEt_3, $CHCl_3$, 0°C; 90%) to provide the dibromide **15** (mp 76–77 °C). Treatment of **15** with DBU (10 equiv of DBU, benzene, 35 °C, 3 days) afforded, after chromatography,[15] the desired hexahydronaphthalene **2** (51%) whose UV and ^1H and ^{13}C NMR spectra[12] are in accord with the assigned structure.

In summation, a viable and stereospecific route to the hexahydronaphthalene **2** has been established. Consequently, we are developing methodology for the synthesis of the lactone moiety of compactin (**1**) and the ultimate coupling of the two units in order to complete the total synthesis.

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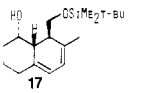
Registry No. **2**, 80106-18-9; **3**, 80106-19-0; **4**, 80106-20-3; **5**, 50999-04-7; **6**, 80106-21-4; **7**, 80106-22-5; **8**, 5837-72-9; **9**, 80106-23-6; **10**, 80106-24-7; **11**, 80106-25-8; **12**, 80106-26-9; **13**, 80106-27-0; **14**, 80126-93-8; **15**, 80106-28-1; **17**, 80106-29-2; *tert*-butyl acetate lithium anion, 53503-61-0; *E,E*-octa-4,6-dien-1-ol, 80106-30-5; (±)-(1α,2α,4aβ,8aα)-decahydro-8-hydroxy-2-methyl-1-naphthalenemethanol, 80106-31-6.

Supplementary Material Available: Full ^1H NMR data for compounds **2**, **3**, **9**, **10**, and **17** and ^{13}C NMR data for compounds **2** and **12** (2 pages). Ordering information is given on any current masthead page.

(10) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(11) M. Jacobson, *J. Am. Chem. Soc.*, **77**, 2461 (1955).
(12) All new compounds reported herein are racemic (where appropriate) and exhibit satisfactory spectral (IR, NMR, UV), analytical, and/or high-resolution mass spectral characteristics.
(13) Prepared by selective ozonolysis of methyl sorbate according to the procedure of P. L. Stotter and J. B. Eppner, *Tetrahedron Lett.*, 2417 (1973).
(14) Bromination of the diol provides a dibromo diol (mp 141–142 °C) in 60% yield accompanied by other uncharacterized products.
(15) An isomeric diene, **17**, assigned the structure below based on the



17

^1H NMR spectrum,[12] is also produced (5% yield). This isomer presumably arises via either E1 dehydrobromination of **16** or isomerization of axial allylic bromide **16** to the equatorial isomer followed by E2 dehydrobromination.

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