for III containing doubly bridging hydrogens would have a maximum coordination number of eight. The structure of III clearly demonstrates the variability in coordination number that can occur in organo-f-element complexes even when radial sizes and ligands are very similar.[31]

Like I, complexes II and III can also be used to initiate the catalytic hydrogenation of alkynes. Interestingly, the catalytic rates for I–III differ substantially, suggesting that several catalytic pathways are possible in this system. II displays the highest turnover rates, 1.5 min^{-1} $[Sm]^{-1}$ for $C_6H_5C{\equiv}CC_6H_5$ to $C_6H_5CH_2CH_2C_6H_5$ and 3.7 min^{-1} $[Sm]^{-1}$ for 3-hexyne to hexane, which are the fastest observed for a homogeneous f-element-based system.[6,32] Mechanistic and structural studies on this system are continuing.

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Supplementary Material Available: Tables of bond distances, angles, final fractional coordinates, and thermal parameters (3 pages). Ordering information is given on any current masthead page.

(31) Consistent with this variability, the differences in M···M distances, 0.102 Å, and in M–C(η^5) distances, 0.075 Å, between III and the thorium complex are much greater than the difference in their ionic radii, 0.026.[26]

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Total Synthesis of the Hypocholesterolemic Agent (+)-Compactin

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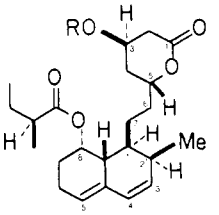
Compactin (**1**),[1] a fungal metabolite isolated from the strains

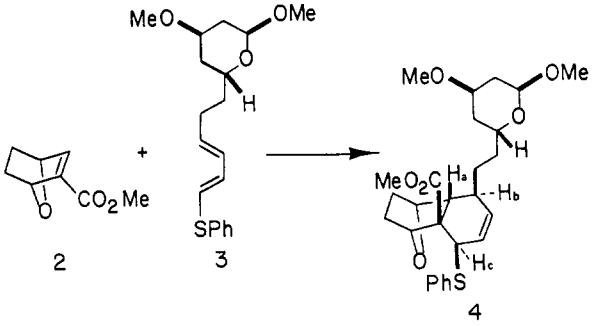


I, R = H

18, R = Me

of *Penicillium brevicompactum*, has been the object of intense synthetic activity[2,3] since the disclosure[4] that it is a potent competitive inhibitor of rat liver microsomal 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-controlling enzyme in cholesterol biosynthesis. We detail in this communication a highly convergent, enantiospecific total synthesis of (+)-compactin.

Our strategy for the construction of compactin centered around the Diels–Alder reaction between the chiral dienophile **2** and the



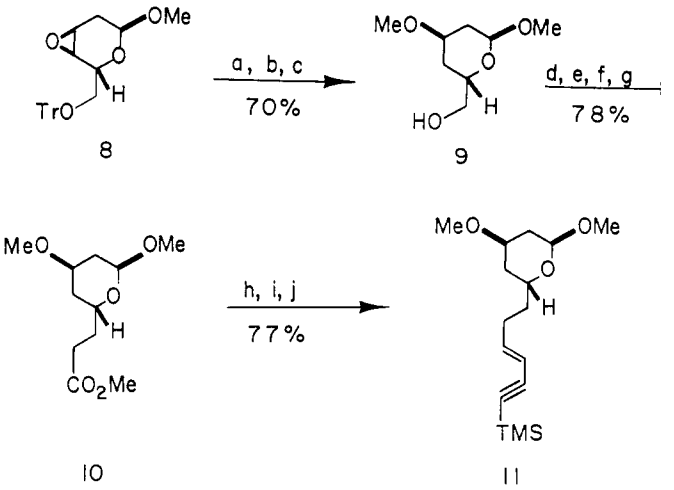
chiral diene **3**, which provides in a single operation the intact carbon framework (cf. **4**) of **1**.

Synthesis of the 7-oxabicyclo[2.2.1]heptane derivative **2** in chiral form commenced with the known Diels–Alder adduct **5**,[5] readily

5 6 R = H 7 R = Me

available from furan and ethyl β-nitroacrylate.[6] Reduction ($K^+{}^-OOCN{=}NCOO^-K^+$, MeOH, AcOH, 0 °C, 8 h) of the double bond in **5** followed by hydrolysis (10% KOH, THF, 0 °C) of the ester gave rise to a 92% yield of racemic acid **6**, mp 164–166 °C. Treatment of **6** with D(−)-α-phenylglycinol in acetonitrile containing 1.2 equiv of dicyclohexylcarbodiimide gave rise to a near quantitative yield of a diastereomeric mixture of sensitive amides, which were readily separated by HPLC.[7] The less polar

Scheme I. Preparation of Enyne **11**[a]



[a] (a) $LiAlH_4$, Et_2O, −10 °C, 3.5 h; (b) NaH, THF, MeI, 18 h; (c) Na, NH_3, −78 °C (30 min) → −33 °C (30 min); (d) TsCl, py, 11 h; (e) NaI, MEK, reflux, 4 h; (f) $C_6H_5SO_2CH_2CO_2Me$, Me_2SO Me_2SO^- Na^+, 80 °C, 9 h; (g) 6% Na(Hg), MeOH, Na_2HPO_4, 0 °C, 15 min; (h) $LiAlH_4$, Et_2O, 0 °C, 15 min; (i) $CrO_3{\cdot}2py$, CH_2Cl_2, 0 °C, 20 min; (j) $(C_6H_5)_3P^+CH_2C{\equiv}C(Me_3Si)$ Br^-, BuLi, THF, −78 °C.

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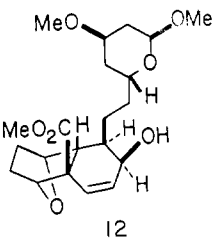
amide was directly treated with 3 M hydrochloric acid in methanol for 3 h at 65 °C giving rise (48% overall from acid **6**) to methyl ester **7**, $[\alpha]_D$ −82.6° (*c* 3.05, $CHCl_3$).[8] Exposure of **7** to DBU in refluxing methylene chloride (2 h) provided in 75% yield dienophile **2**, $[\alpha]_D$ +179.4° (*c* 1.88, $CHCl_3$).

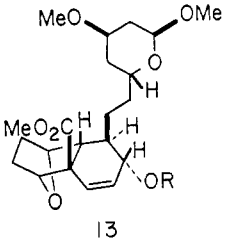
Elaboration of the carbohydrate-based diene component **3** originated with epoxy trityl (Tr) ether **8** (Scheme I), which has been previously prepared from commercially available tri-*O*-acetyl-D-glucal.[9] Opening of epoxide **8** proceeded with 92% selectivity giving rise, after methylation and detritylation, to alcohol **9**, $[\alpha]_D$ +132.1° (*c* 1.24, $CHCl_3$). Alkylation of the iodide derived from **9** with methyl phenylsulfonylacetate and subsequent desulfonylation[10] produced in 78% overall yield methyl ester **10**, $[\alpha]_D$ +110.6° (*c* 2.04, $CHCl_3$). Condensation of the aldehyde derived from ester **10** (Scheme I) with [(trimethylsilyl)propargylidene]-triphenylphosphorane[11] generated the *trans*-enyne **11**, $[\alpha]_D$ +84.3° (*c* 1.90, $CHCl_3$). Cleavage (Bu_4NF, THF, 0 °C, 10 min) of the silyl group in **11** and addition of benzenethiol across the terminal acetylene unit (C_6H_5SH, HMPA, AIBN (catalyst), 150 °C, 5 min) provided diene **3** in 94% overall yield as a 3(*E*):2(*Z*) mixture about the vinyl sulfide carbon–carbon bond.[12]

With both the dienophile **2** and the diene component **3** available as enantiomerically pure substances, the stage was set for construction of the carbon framework of compactin. Endo addition of **3** (3.0 equiv) to the exo face of the oxabicyclic dienophile **2** (1.0 equiv; toluene, 2,6-di-*tert*-butyl-4-methylphenol (0.4 equiv), sealed tube, 125 °C (bath temperature), 14 h) afforded adduct **4**, $[\alpha]_D$ +61.6° (*c* 1.35, $CHCl_3$), in 70% yield. The stereochemical assignment for **4** follows from its 360-MHz NMR spectrum, which reveals H_a as a doublet (δ 2.13) with J_{ab} = 9.36 Hz and H_c as a broad singlet (δ 3.88).

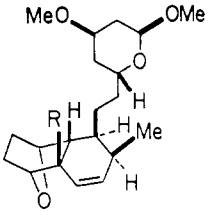
Oxidation (MCPBA, CH_2Cl_2, −78 °C) of sulfide **4** did not afford any allylic sulfoxide, but instead gave way directly to the corresponding rearranged allylic sulfenate as the sole product. Treatment with trimethylphosphite (MeOH, reflux, 2.5 h) led to the isolation of allylic alcohol **12**, $[\alpha]_D$ +36.6° (*c* 2.55, $CHCl_3$), in 70% overall yield. The inability to isolate the sulfoxide derived from sulfide **4** necessitated that our strategy for the introduction of the C(2′) methyl group be altered. Toward this end, allylic alcohol **12** was subjected to a Mitsunobu reaction[13] (DEAD, $PhCO_2H$, Ph_3P, THF, 15 min) so as to permit inversion of configuration about C(2′). As a consequence, allylic benzoate **13** (R = COPh), $[\alpha]_D$ −98.9° (*c* 3.04, $CHCl_3$), which was obtained in 93% yield, was hydrolyzed (1.9 M NaOMe, MeOH, 2.5 h) giving rise (85%) to allylic alcohol **13** (R = H),[14] mp 124–125 °C, $[\alpha]_D$ −40.8° (*c* 1.61, $CHCl_3$). Acetylation (Ac_2O, Et_3N, DMAP, CH_2Cl_2) of **13** (R = H) followed by reaction with lithium dimethylcuprate at −10 °C in ether gave rise exclusively to **14**, $[\alpha]_D$ +59.1° (*c* 1.56, $CHCl_3$), in 86% overall yield.



12

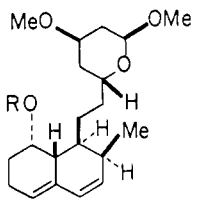


13



14, R = CO_2Me

15, R = CH_2OH



16, R = H

17, R = 

Reduction ($LiAlH_4$, Et_2O, 0 °C, 30 min) of ester **14** generated alcohol **15**, which was subjected to a Grob fragmentation. Treatment (3 h) of **15**, $[\alpha]_D$ +87.9° (*c* 2.03, $CHCl_3$), with potassium hydride in refluxing toluene afforded alcohol **16**, $[\alpha]_D$ +219.2° (*c* 1.20, $CHCl_3$), in 40% overall yield from **14**. Acylation of **16** with 3.0 equiv of (*S*)-2-methylbutyric anhydride[15] in methylene chloride containing 1.5 equiv of 4-(dimethylamino)-pyridine and 4.0 equiv of triethylamine proceeded at room temperature over a 16-h period in near quantitative yield, giving rise to **17**, $[\alpha]_D$ +247.8° (*c* 1.48, $CHCl_3$).

Exposure (20 min) of **17** to 10% hydrochloric acid in tetrahydrofuran (3:5) at 45 °C and subsequent oxidation with Fetizon's reagent (Ag_2CO_3, benzene, reflux, 4 h) provided (71%) lactone **18**, mp 100–101 °C, $[\alpha]_D$ +243.1° (*c* 1.14, $CHCl_3$), which was identical (mp, NMR, IR, $[\alpha]_D$, TLC, HPLC) in all respects with a sample of **18**[16] derived from natural compactin. Demethylation (BBr_3, CH_2Cl_2, −23 °C, 6 h) of **18** provided (31%) (+)-compactin, whose physical and spectral properties were found to be identical with those of an authentic sample of **1**.

Acknowledgment. This investigation was supported by Public Health Service Research Grant CA 28865 from the National Cancer Institute. We are indebted to Professor E. H. Goh (Department of Pharmacology, Indiana University) for a generous gift of natural compactin. We thank Dr. M. Ubakata and P. Hipskind for experimental assistance during the early stages of this investigation. The 360-MHz NMR instrument (Nicolet) used in the above studies was purchased in part through funds provided by the National Science Foundation (Grant CHE-81-05004).

Supplementary Material Available: Spectral and analytical data for **1–4**, **7**, and **9–18** (5 pages). Ordering information is given on any current masthead page.

(7) The HPLC separation was carried out on a Waters Prep LC/system 500A using two Prep PAK-500/silica cartridges (57 mm × 30 cm; 7:3 ethyl acetate/hexane, flow rate 300 mL/min). The retention times of the less polar and more polar amides were 4.5 and 11.5 min, respectively.

(8) The more polar diastereomer gave rise to the corresponding antipodal methyl ester, $[\alpha]_D$ +78.3° (*c* 3.78, $CHCl_3$).

(9) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439.

(10) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(11) Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, 1495.

(12) The *E*:*Z* mixture of vinyl sulfides is of no consequence since the *Z* isomer does not react with **2**.

(13) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427.

(14) The structure of **13** (R = H) was unambiguously established by single-crystal X-ray analysis. Details will be published elsewhere.

(15) (*S*)-2-Methylbutyric anhydride was prepared according to the procedure briefly outlined in ref 2a.

(16) Methylated compactin **18** was prepared by treatment of a solution of natural compactin in dry ether containing suspended silicAR CC-7 with gaseous diazomethane [Cf.: Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, *20*, 4405].