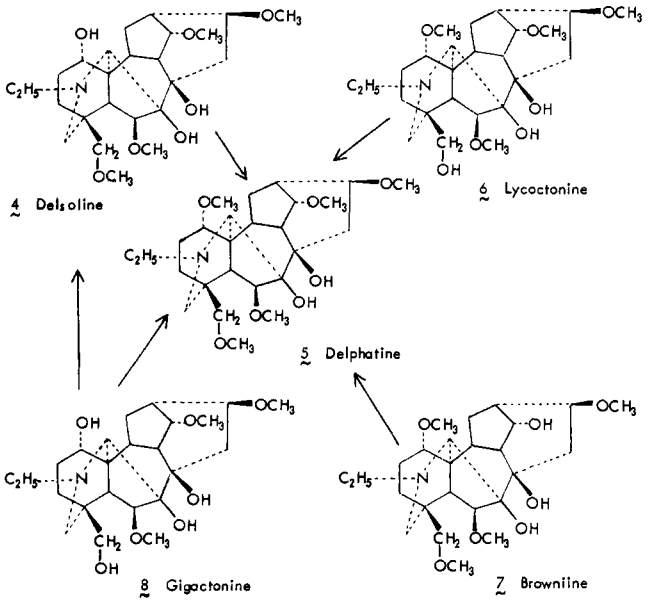

dimethylated product of gigactonine and that given for delphatine, prepared from lycoctonine, are so similar that the minor differences in their chemical shifts could result from solvent effects. On the basis of our results, it seems likely that the dimethlated product prepared from gigactonine and the sample of delphatine prepared from lycoctonine are identical.

Of interest is the fact that there is not a single, naturally occurring C_{19}-diterpenoid alkaloid which bears a C(1)-β-OCH_3 group.[17]

(17) The configuration of the C(1)-methoxyl group must be also revised from β to α in delbiterine (16-demethyldelphatine) and in elatine (7,8-methylenedioxy)methyllycaconitine.

Total Synthesis of (+)-Compactin (ML-236B)

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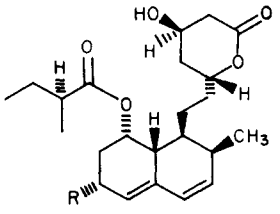
Compactin[1] (**1**) and ML-236B are identical fungal metabolites isolated from strains of *Penicillium brevicompactum* and *Penicillium citrinum*, respectively. Compactin has been shown to be a potent competitive inhibitor[2] of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-controlling enzyme in cholesterol biosynthesis.

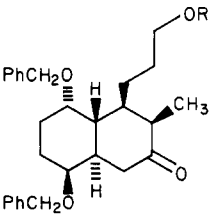


1, R = H
2, R = CH_3

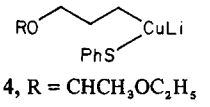
(1) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(2) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323.

The apparent efficacy of **1** as a therapeutic agent for the treatment of hypercholesterolemia in humans and the enhanced activity of mevinolin, **2**, in in vitro animal models precipitated our interest to devise general synthetic methodologies for the preparation of this important family of substituted hexahydronaphthalene lactones. Herein, we report the first synthesis of (+)-compactin.

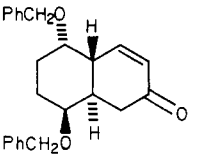
Central to our synthetic plan is the development of a viable route to **3**. This key intermediate not only possesses strategically situated oxygen functionalities for the eventual elaboration of the *transoid* conjugated diene but also allows the construction of the highly sensitive β-hydroxy lactone of **1** during the final stages of the synthetic sequence. We projected that **3** might be prepared by the combination of conjugate addition of the functionalized mixed cuprate **4**[3,4] to the enone **5**[5] and trapping of the resulting kinetic enolate with a suitable electrophile. In turn, **5** may be derived from the readily available *trans*-dione (**6**).[6]



3, R = $CHCH_3OC_2H_5$

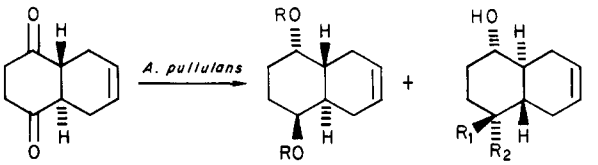


4, R = $CHCH_3OC_2H_5$



5

Since chemical reduction of **6** with diisobutylaluminum hydride afforded a statistical mixture of racemic diastereomers, we decided to effect the reduction of **6** into **7** by using microbial methods. Although microbiological conversion of **6** to **7** had been reported,[7] the yield of this transformation was very low. On the other hand, exposure of **6** to *Aureobasidium pullulans* NRRL Y-12610[8] afforded **7**, in 33% yield, accompanied by **8** (22%) and (±)-**9** (45%). The optical purities of **7** and **8** were confirmed by their oxidation with Jones reagent to give (−)-**6** and (+)-**6**, respectively. The inherent symmetry element (C_2 axis) in this chiral intermediate, **7**, and its ready accessibility via microbial methods markedly facilitated the ensuing transformations. Treatment of



(±)-**6**

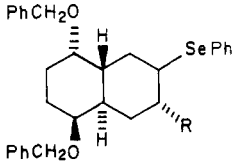
7, R = H
10, R = CH_2Ph

8, R_1 = OH; R_2 = H
9, R_1 = H; R_2 = OH

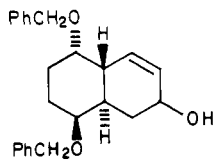
7 with 2 equiv of NaH in Me_2SO at 25 °C, followed by the addition of $C_6H_5CH_2Cl$[9] gave **10** (99%) as an oil, which upon reaction with phenylselenenyl bromide (HOAc/KOAc, 25 °C, 1 h) furnished **11**. Saponification of **11** [1.2 equiv of KOH/CH_3OH–ether (4:1), 25 °C, 2 h] afforded **12** (89%), which was oxidized to the corresponding selenoxide (H_2O_2/THF, 25 °C, 2.5 h). The latter undergoes smooth elimination on heating at 55 °C for 2 h to give the allylic alcohol **13**, which without isolation was subjected to Jones oxidation to give **5** (71% from **10**).

(3) Eaton, P. E.; Cooper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947.
(4) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662.
(5) Crossley, N. S. *Tetrahedron Lett.* **1971**, 3327.
(6) Van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969**, *91*, 7315. Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1620.
(7) Aklin, W.; Prelog, V.; Schenker, F.; Serdarevic, B.; Walter, P. *Helv. Chim. Acta* **1965**, *48*, 1725.
(8) We thank Dr. C. P. Kurtzman of Northern Regional Research Center in Peoria for the identification of this soil isolate (Bu 103).
(9) Iwashige, T.; Saeki, H. *Chem. Pharm. Bull.* **1967**, *15*, 1803.

0002-7863/81/1503-6538$01.25/0

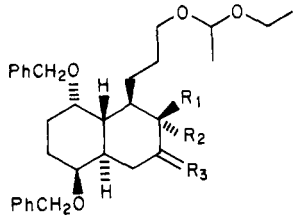


11, R = OAc
12, R = OH

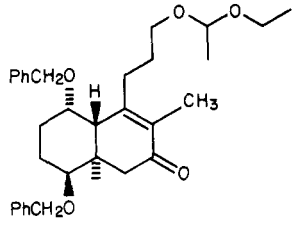


13

When **5** was reacted with **4** (THF, −20 °C, 30 min), followed by the addition of excess methyl iodide (DME,[10] −20 °C, 15 min), **14** (80%) was obtained. To ascertain the stereochemistry of the newly introduced methyl substituent, the conjugate addition was repeated but the intermediary copper–lithium enolate was alkylated with a slight excess of gaseous formaldehyde (THF, −78 °C, 30 min) to give a mixture (67%) of **15** and **16**. This mixture was mesylated ($MsCl/Et_3N/CH_2Cl_2$, −5 °C, 30 min) and the crude mesylate was subjected to elimination (DBU/benzene, 25 °C) to yield **17** (95% from **14**). When **17** was hydrogenated (10% Pd/C, H_2, EtOH), two epimers **3** and **14** were formed (75% yield) in a 55:45 ratio, accompanied by 20% of **18**. These were separated by repeated silica gel column chromatography (benzene/EtOAc, 93:7). In the presence of sodium methoxide in methanol (24 h, 25 °C), both epimers equilibrated to give a 9:1 mixture of **14** and **3**. Because **17** has a strong tendency to undergo isomerization on the surface of palladium metal, the hydrogenation of **17** was later conducted in the presence of pyridine[11] to minimize this undesirable side reaction. To our delight, under this condition the desired axial epimer **3** was obtained in 81% yield; concomitantly, formation of the equatorial epimer **14** was significantly diminished (10%).

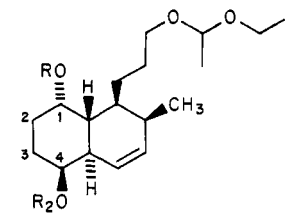


14, R_1 = H; R_2 = CH_3; R_3 = O
15, R_1 = H; R_2 = CH_2OH; R_3 = O
16, R_1 = CH_2OH; R_2 = H; R_3 = O
17, R_1 = R_2 = CH_2; R_3 = O
19, R_1 = CH_3; R_2 = H;
R_3 = N–N(H)–Ph–CH_3

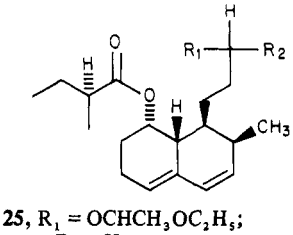


18

Condensation of the ketone **3** with tosyl hydrazide[12] (anhydrous EtOH, 25 °C, 7 h) afforded **19**, which after removal of the solvent was treated with 10 equiv of LDA (THF, −78–0 °C) to yield **20** (62% from **3**). Debenzylation (Li/liquid NH_3) of **20** went smoothly giving **21** in quantitative yield. Attempts to selectively monoacylate **21** using 1 equiv of (*S*)-2-methylbutyric anhydride[13] (MBA) (pyridine/DMAP, 25 °C, 16 h) gave **22** as the major product.[14] Hence, **21** was treated with an excess of MBA yielding **23** (97%). When the latter was hydrolyzed (20-fold excess KOH/EtOH, 25 °C, 16 h), **24** (63%) and **22** (6.6%) were obtained, accompanied by **23** (6.5%) and a trace of diol **21**. Mesylation (MsCl/pyridine, 0 °C, 8 h) of **24**, followed by elimination (DBU/pyridine, 115 °C, 3 h) furnished **25** (86%). The protecting group was removed by hydrolysis (HOAc/THF/H_2O, 3:2:1) to yield **26**, which upon oxidation (PCC/CH_2Cl_2, 25 °C, 2 h) gave the aldehyde **27** (60%).



20, R_1 = R_2 = CH_2Ph
21, R_1 = R_2 = H
22, R_1 = H; R_2 =
C(=O)CH(CH_3)C_2H_5
23, R_1 = R_2 =
C(=O)CH(CH_3)C_2H_5
24, R_1 = C(=O)CH(CH_3)C_2H_5;
R_2 = H



25, R_1 = $OCHCH_3OC_2H_5$;
R_2 = H
26, R_1 = OH; R_2 = H
27, R_1 = R_2 = O
28, R_1 = OH; R_2 =
$CH_2C(=O)CH_2CO_2CH_3$
29, R_1 = $CH_2C(=O)CH_2CO_2CH_3$;
R_2 = OH

The lactone was incorporated into the bicyclic nucleus, **27**, by reacting **27** with the dianion of methyl acetoacetate (NaH/*n*-BuLi/THF, 0 °C, 15 min)[15] to yield two diastereomeric alcohols **28** and **29** (68%). Because this mixture resisted separation by TLC and HPLC, these two δ-hydroxy-β-keto esters were reduced [excess $Zn(BH_4)_2$, 0 °C, 1 h] to two pairs of β,δ-dihydroxy esters (63%), **30** and **31** (3:2) [EtOAc/hexane (3:2)]. The less polar pair of the β,δ-dihydroxy esters, **30** was separated from **31** by chromatographing the mixture over a silica gel column (acetone/$CHCl_3$, 1:9). Lactonization (*p*-TsOH·H_2O/benzene, 25 °C, 30 min) of **30** afforded two β-hydroxy lactones (65%) from which **1** (30 mg) was isolated by HPLC.[16] The synthetic specimen was found to be identical ($[\alpha]_D$, IR, HPLC, NMR, MS) with natural (+)-compactin.

This synthetic sequence leading to compactin can also be adapted to the synthesis of mevinolin and other analogues, either directly or by chemical modification of intermediates at varying levels of functional and structural developments. These studies and further refinements of this scheme are currently under investigation.

Acknowledgment. This research was supported in part by a grant from the National Institutes of Health (HL 25772). We thank Dr. A. G. Brown of Beecham for a sample of natural compactin and Dennis Ditullio for conducting the microbiological work.

Supplementary Material Available: TLC, mp, IR, 90-MHz ^1H and ^{13}C NMR, and $[\alpha]_D$ data of new compounds (4 pages). Ordering information is given on any current masthead page.

(10) Coates, R. M.; Sandefur, L. O. *J. Org. Chem.* **1974**, *39*, 275.
(11) Djerassi, C.; Romo, J.; Rosenkranz, G. *J. Org. Chem.* **1951**, *16*, 754.
(12) Commercial tosyl hydrazide must be pretreated with Et_3N to neutralize a trace of acid, thus preventing the hydrolysis of the protecting group in **19**.
(13) (*S*)-2-Methylbutanol (Aldrich), $[\alpha]^{25}_D$ −5.8° (neat) was oxidized (Von E. Doering, W.; Aschner, T. C. *J. Am. Chem. Soc.* **1953**, *75*, 393) to (*S*)-2-methylbutyric acid, $[\alpha]^{25}_D$ +18° (neat), which was converted (DCC/CH_2Cl_2, 0 °C, 3 h) to (*S*)-2-methylbutyric anhydride, bp 60 °C (0.2 mm); $[\alpha]^{25}_D$ +30.2° (neat, d = 0.9318) in 97% yield.
(14) The assignment of the position of the ester was based on the observation that mesylation and subsequent elimination of **22** gave a diene system whose NMR pattern was completely different from that of compactin.
(15) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(16) HPLC separation was carried out on a Waters radial compression module (RCM-100) with a radial-Pak 5μ silica gel cartridge (0.8 × 10 cm) (mobile phase, $CHCl_3$; flow rate, 5 mL/min). The retention times of compactin and the second diastereomer in **30** were 16.4 and 21.8 min, respectively.