T_1; however, fast exchange with an η^2-H_2 having a short T_1 could certainly decrease the observed average value. One can imagine a system possessing a T_1 borderline between those of η^2-H_2 and dihydride protons consisting of an equilibrium between a dihydride and an unobserved dihydrogen.

Supplementary Material Available: Solutions to the Bloch equations in the presence of exchange and a description of the fitting procedure (3 pages). Ordering information is given on any current masthead page.

Total Synthesis of Natural Ambruticin

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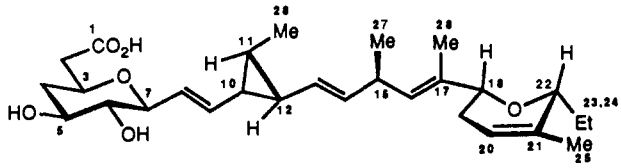
The structurally unique $C_{28}H_{42}O_6$ antifungal antibiotic ambruticin (**1**)[1] is systemically active against the diseases histoplasmosis and coccidiomycosis.[2,3] Its absolute configuration was established by synthesis of ozonolysis fragments **2** and **3a,b** from arabinose and resolved Feist's acid, respectively,[4] and confirmed by preparation of **3b** from citronellal.[5] Ambruticin has elicited



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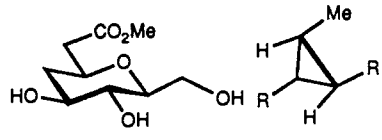


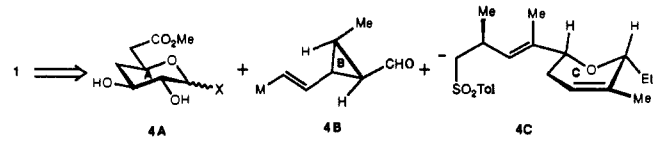
2

3a R = CH_2OH

3b R = CO_2H

considerable synthetic interest,[6] notably by Sinaÿ.[7] We now report the first total synthesis of (+)-ambruticin by a convergent strategy retrosynthetically represented in Figure 1, where X is a leaving group and M an appropriate metal.

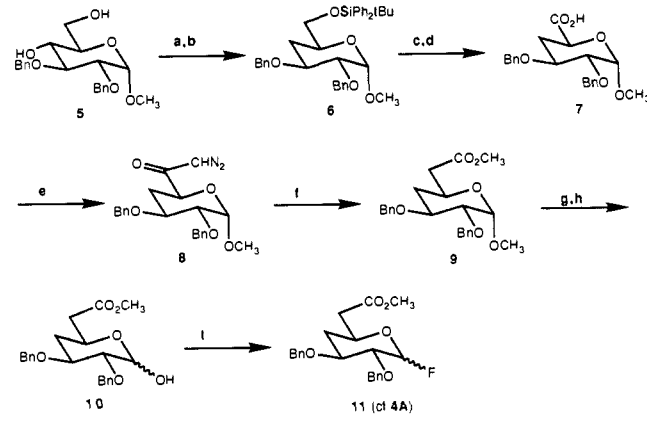
The C_7 deoxypyranose synthon **4A** was prepared in 10 steps (26% overall yield) from the methyl α-glucopyranoside **5**[8] of



4A **4B** **4C**

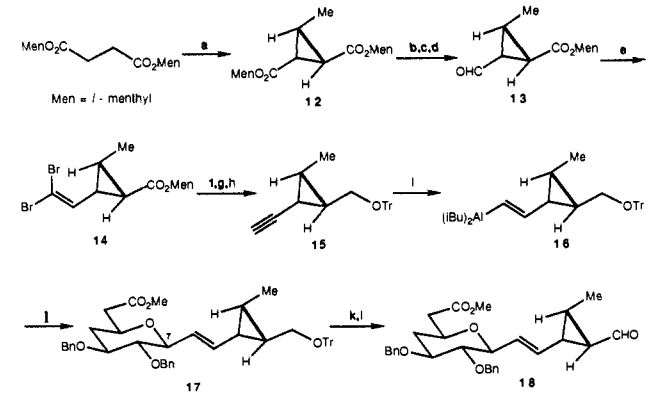
Figure 1.

Scheme I[a]



[a] (a) *t*-$BuPh_2SiCl$, imidazole, DMF, room temperature, 2 h, 99%; (b) Im_2CS, toluene, reflux, 8 h; Bu_3SnH, toluene, reflux, 16 h, 77%; (c) Bu_4NF, THF, room temperature, 18 h, 95%; (d) PDC, DMF, room temperature, 20 h, 88%; (e) $(COCl)_2$, DMF (cat.), CH_2Cl_2, room temperature, 2 h; CH_2N_2, Et_2O, 0 °C, 30 min, 78%; (f) *hν*, MeOH, 30 °C, 48 h, 68%; (g) Ac_2O, H_2SO_4 (cat.), -20 °C, 10 min, 88%; (h) MeONa, MeOH, 0 °C, 10 min, 97%; (i) Et_2NSF_3, CH_2Cl_2, -30 °C, 10 min, 92%.

Scheme II[a]



[a] (a) Lithium 2,2,6,6-tetramethylpiperidide, THF, 0 °C, then 1-bromo-1-chloroethane, -78 °C, 3 h, 45%; (b) 10% KOH (EtOH/H_2O, 9:1), room temperature, 83%; (c) B_2H_6/THF, 0 °C → room temperature, 8 h, 100%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C → -30 °C, 96%; (e) Ph_3P, CBr_4, CH_2Cl_2, 0 °C, 30 min, 98%; (f) DIBAL, toluene, 0 °C, 30 min, 90%; (g) TrCl, DMAP, Et_3N, CH_2Cl_2, room temperature, 72 h, 90%; (h) nBuLi, THF, -78 °C, 10 min, 92%; (i) DIBAL, hexane, 50 °C, 2 h; (j) **11**, toluene, -20 °C → room temperature, 30 min, 49%; (k) pTSA (cat.), MeOH/CH_2Cl_2 (1:1), room temperature, 2 h, 92%; (l) Dess-Martin's periodinane, CH_2Cl_2, room temperature, 30 min, 90%.

Scheme I. Key steps included Barton deoxygenation[9] of the C-4 hydroxyl, photochemical Arndt-Eistert homologation[10] of **7**, and finally Et_2NSF_3 generation of a 73:27 β:α ratio of the glycosyl fluorides **11**.[11]

The cyclopropane precursor to synthon **4B** was synthesized (Scheme II) by an intriguing extension of Yamamoto's dianion chemistry,[12] whereby $CH_3CHBrCl$ as electrophile condenses with

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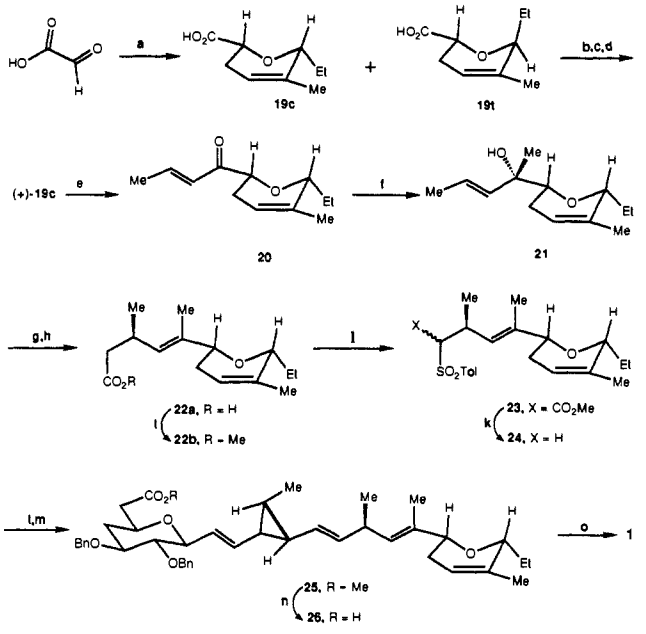
Scheme III[a]



[a] (a) 3-Methyl-1,3-hexadiene, hydroquinone (cat.), $CHCl_3$, sealed tube, 120 °C, 12 h, 81%; (b) 2,4'-dibromoacetophenone, KF, DMF, room temperature, 3 h, then 100 °C, 30 min, 53%; (c) Zn, AcOH (glacial), room temperature, 8 h, 90%; (d) (+)-α-methylbenzylamine, MeOH/Et_2O, crystallization, 32%; (e) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C → room temperature, 2 h, then *trans*-propenyltrimethyltin, $PhCH_2PdCl(PPh_3)_2$ (cat.), HMPA, 70 °C, 3 h, 90%; (f) MeMgBr, THF, 0 °C, 2 h, 92%; (g) Ac_2O, DMAP, Et_3N, CH_2Cl_2, room temperature, 72 h. 72%; (h) LDA, THF, −78 °C, then TBSCl, THF/HMPA, −78 → 60 °C, 1.5 h, then H_3O^+, 61%; (i) CH_2N_2, Et_2O, room temperature, 92%; (j) LDA, THF, −78 °C, then PTSF, THF, −78 °C → room temperature, 24 h, 43%; (k) $(Me)_4N^+{}^-OAc$, HMPA, 100 °C, 17 h, 71%; (l) nBuLi, Et_2O/hexane, 0 °C → −42 °C, then **18**, −42 °C, 2 h, 51%; (m) Na(Hg) 6%, MeOH/THF (1:1), −35 °C, 3.5 h, 63%; (n) LiOH, THF/H_2O (3:1), room temperature, 18 h, (o) Li, liquid NH_3/EtOH (5:1), −78 °C, 30 min, 63% from **25**.

apparently complete diastereoselection giving diester **12** (configuration of **12** established by hydrolysis to diacid **3b**, or reduction to diol **3a**). Selective hydrolysis of **12** led ultimately to the acetylene **15**, which on hydroalumination to **16** and condensation with **11** gave 49% of the desired alkenyl β-*C*-glycoside **17**.[13] Detritylation and Dess–Martin oxidation[14] gave **18** in 10 steps and 24% yield from ester **12**.

The C_{14} right half was prepared (Scheme III) by starting with thermal Diels–Alder addition of (*E*)-3-methyl-1,3-hexadiene[15] with glyoxylic acid, producing a 4:1 ratio of **19c**/**19t**.[16] Resolution with (+)-$PhCH(CH_3)NH_2$ gave the requisite (+)-**19c**, $[\alpha]^{21}_D$ = +169.4° (*c* 0.85, EtOH), >98% ee.[17] Its acid chloride gave (*E*)-enone **20**, which underwent chelated Cram MeMgBr addition to yield **21**, converted by Ireland–Claisen rearrangement of its acetate to acids with **22a** predominating by a 12:1 ratio.[7a] Ester **22b** reacted with *p*-$MeC_6H_4SO_2F$[18] to yield **23**, which on decarbomethoxylation[19] produced **24** (cf. **4C**) in seven steps (10%) from (+)-**19c**.

Julia condensation of sulfone **24** with aldehyde **18** gave 13-(*E*)-tetraene **25**, accompanied by 8% of the 13(*Z*) isomer. Tetraene **25** was saponified, and careful Birch debenzylation[20] produced the diol acid **1** (63% yield from **25**), identical by 300-MHz ^1H NMR, TLC, and $[\alpha]_D$ with natural **1**. Reaction of synthetic **1** with CH_2N_2 gave ambruticin methyl ester, identical in all respects, including FD-MS, with authentic **1** methyl ester. Thus natural (+)-ambruticin has been prepared for the first time in a convergent synthesis from glyoxylic acid (15 steps in the longest sequence).[21]

Supplementary Material Available: Physical, spectral, and analytical data for compounds **6**, **8**, **9**, **11–15**, **17–21**, **22b**, **24**, **25**, synthetic **1**, natural **1**, and their methyl esters (11 pages). Ordering information is given on any current masthead page.

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(13) Cf.: Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 1823 and references therein.

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(15) This diene was prepared by Wittig methylenation of commercially available (*E*)-2-methylpentenal.

(16) **19c** methyl ester showed ^{13}C NMR signals at δ 78.4 (C-2) and 72.4 (C-6); **19t** methyl ester at δ 76.5 (C-2) and 67.9 (C-6). Cf.: Eliel, E.; Manoharan, M.; Pietrusziewicz, K. M.; Hargrave, K. D. *Org. Magn. Reson.* **1983**, *21*, 94. Also: Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787.

(17) The amide from (+)-**19c** and (−)-α-phenylethylamine was homogeneous by GC and ^1H NMR. Acid (−)-**19c** of $[\alpha]^{21}_D$ = −142° (*c* 0.84, EtOH) was reacted with O_3, then H_2O_2/HCO_2H, and then CH_2N_2, to give (L)-dimethyl malate having $[\alpha]^{21}_D$ = −7.31° (*c* 1.92, EtOAc); cf.: Walden, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 386.

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(20) Cf.: Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 963.

(21) We thank Dr. C. J. Wright (Eastman Kodak Research Laboratories) for FD mass spectra and Dr. J. Hodges (Warner Lambert/Parke-Davis Co.) for a sample of natural ambruticin. Partial support of this research by Grant CA-18846, awarded by the National Cancer Institute (NIH), is gratefully acknowledged.

Palladium-Catalyzed Reaction of Methyleneoxazolidinones. Intervention of a Palladium Complex of a Y-Shaped $CH_2C(NTs)CH_2$ Molecule as an Isostructure of Trimethylenemethane

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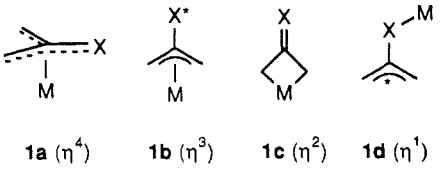
The metal complexes of fully unsaturated Y-shaped molecules, e.g., trimethylenemethane,[1] have been fascinating organic and organometallic chemists. The modes of the metal complexation can be **1a** (η^4), **1b** (η^3), **1c** (η^2), and **1d** (η^1) (see structures) with X representing CH_2 or hetero atoms (an asterisk stands for a radical or ion). The stable complexes of **1a** with X = CH_2[1a,b]



1a (η^4) **1b** (η^3) **1c** (η^2) **1d** (η^1)

and M = Fe, Cr, Mo, Ru, Os, and Ir, with X = O and M = Ru,[2] and with X = S and M = Fe,[3] of **1c** with X = O and M = Ru,[2] Pd,[4] Pt,[5] Os,[6] and Ir,[6] and of **1d** with X = O and M = Fe[7] have

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