between the Sm^{3+} chelate and the carboxylate would account for the relative stereochemistry between the diol stereocenters and the carboxylate. Subsequent intermolecular reduction of the chelate complex by SmI_2 and hydrolysis would produce the observed products.

Several pertinent examples of apparent ketyl addition to Lewis acid complexed carbonyl substrates have been documented,[8b,11] and intramolecular addition of alkyl radicals to unactivated ketones and aldehydes is now even well established.[12] At present, we cannot definitively rule out a two-electron (diketyl) coupling. However, unless a single Sm^{3+} cation complexes both ketyls, one might not expect pure cis diols to be formed by such a two-electron process.[8b]

More will be learned about the detailed mechanism of the reaction through delineation of its scope. Analysis of products derived from functionalized diketone, dialdehyde, and keto aldehyde substrates of a variety of substitution patterns should provide further insight on the factors controlling the cyclization process. At present, the SmI_2-promoted intramolecular pinacolic coupling reaction represents an extremely efficient entry into highly functionalized, stereodefined carbocycles.

Acknowledgment. We are grateful to the National Institutes of Health and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of our programs. We also thank Dr. Paul W. Zinke for performing initial experiments in this area and Curt Haltiwanger for the X-ray crystal structure determinations.

Supplementary Material Available: X-ray crystal structure data for the major diastereomer of **2b** and the two most predominant diastereomers of **2f** (18 pages). Ordering information is given on any current masthead page.

(11) (a) Clerici, A.; Porta, O. *Tetrahedron* **1983**, *39*, 1239. (b) Clerici, A.; Porta, O. *J. Org. Chem.* **1983**, *48*, 1690. (c) Clerici, A.; Porta, O. *J. Org. Chem.* **1987**, *52*, 5099.

(12) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548, and references therein.

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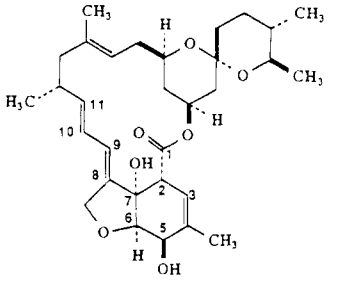
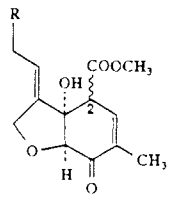
Intramolecular Claisen Condensations. An Efficient Route toward the Avermectins and Milbemycins[†]

Summary: Investigations of novel intramolecular Claisen condensations feature selective deprotonation and enolate formation in a series of dicarbonyl compounds. Ring closures occurred at −78 °C with excellent stereochemical control affording the bicyclic β-hydroxy lactones **13**, **15**, **19**, and **20**. The intramolecular Claisen strategy allows for an efficient preparation of the chiral hexahydrobenzofuran **3** as observed in the potent milbemycin–avermectin family of macrocyclic metabolites.

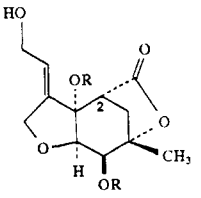
Sir: In recent years we have examined numerous pathways leading toward a fully functionalized hexahydrobenzofuran as exemplified by the southern portion ($C_1 \rightarrow C_{10}$) of milbemycin α_1 (**1**) and avermectin β_{1a}. Recently, several groups have communicated model studies and preliminary results toward this highly oxidized subunit,[1] and a total synthesis of avermectin A_{1a} has been achieved.[2] Our investigations have examined novel intramolecular Claisen condensations to afford the completed cyclohexenone **2**.[3] However, in the course of these studies we became aware of problems of epimerization at C-2 as subsequently detailed by Fraser-Reid and Hanessian for avermectin B_{1a} itself.[4,5] Thus, we sought to prevent isomerization by restricting the C-1 ester as a bicyclic lactone. This report communicates our successful studies of Claisen condensations leading to preparation of the chiral hexahydrobenzofuran **3**, as a potential precursor for total synthesis of the milbemycin–avermectin antibiotics.



Milbemycin α_1 (1)



2



3 R = CH_2OCH_3

Our route begins, as illustrated in Scheme I with the readily available 2,3-*O*-isopropylidene-L-erythose **4** as obtained in three steps from L-rhamnose in 71% overall yield following the literature procedures.[6,7] Reaction with

(1) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1565. Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986**, *27*, 291. Hanessian, S.; Beaulieu, P.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 5071. Barrett, A. G. M.; Capps, N. K. *Tetrahedron Lett.* **1986**, *27*, 5571. For a review of earlier work in this area: Davies, H. G.; Green, R. H. *Nat. Prod. Chem.* **1986**, *3*, 87. After completion of our work, several groups have communicated their advances in this area. Danishefsky, S.; Armistead, D. M. *Tetrahedron Lett.* **1987**, *42*, 4959. Jung, M. E.; Usui, Y.; Vu, C. T. *Ibid.* **1987**, *42*, 5977. White, J. D.; Dantanarayana, A. P. *Ibid.* **1987**, *42*, 6417.

(2) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117, 8119.

(3) Sodium borohydride reduction of the C_5 ketone of **2** is known to stereoselectively yield the desired β-alcohol. Mishima, H.; Junya, I.; Muramatsu, S.; Ono, M. *J. Antibiot.* **1983**, *36*, 980. Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M. *J. Antibiot.* **1983**, *36*, 980. Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M. *J. Antibiot.* **1983**, *36*, 991. Furthermore, we had recognized that the presence of the C_5 ketone is essential to avoid facile isomerization of the carbon double bond into conjugation with the C_1 ester.

(4) Several years ago we had observed selective MnO_2 oxidation of the C_5 hydroxyl of ivermectin in ether (82%) followed by acid hydrolysis of the disaccharide moiety (1% H_2SO_4 in MeOH; 83%), and saponification of the macrocyclic lactone (LiOH, THF in aqueous MeOH) to afford approximately a 1:1 mixture of the separable C-2 epimeric carboxylic acids. No products of double bond migration or decarboxylation were obtained. Macrocyclic lactonization of the 7,13,19-trihydroxy 2α-carboxylic acid (using 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate) gave only esterification at the C-19 alcohol, producing a 3.5:1 ratio of natural to C-2 epimeric lactones. We thank Dr. Santi Sakdarat for conducting these experiments.

(5) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J. *J. Am. Chem. Soc.* **1987**, *109*, 933. See also; Hanessian, S.; Dubé, D.; Hodges, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 7063.

(6) For preparation of the acetonide of L-rhamnose (86% yield): Baker, B. R.; Hewson, K. *J. Org. Chem.* **1957**, *22*, 966.

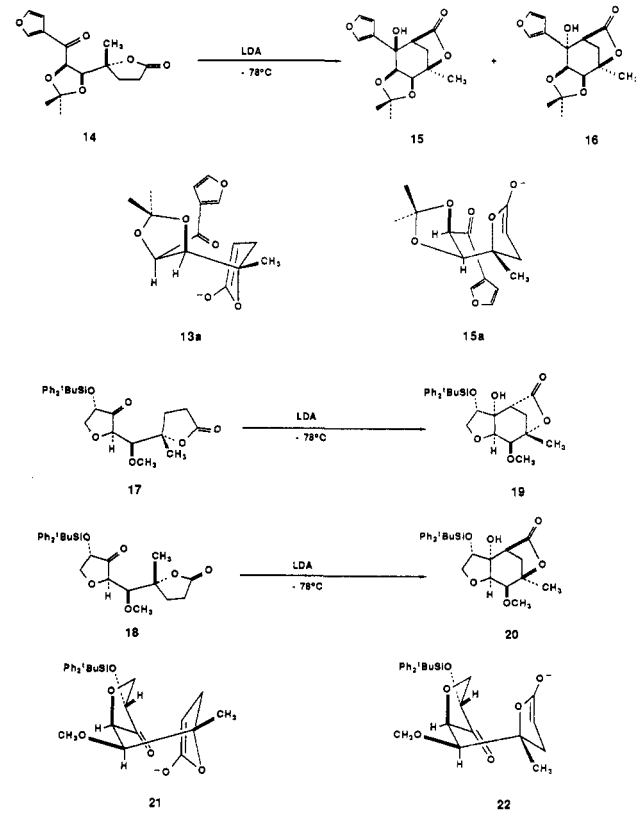
[†] Date of original receipt at the *Journal of the American Chemical Society*: August 6, 1987.

0022-3263/88/1953-2134$01.50/0

methyl magnesium chloride produced diol **5** as the result of a highly stereoselective, chelation-controlled addition (>95:5). Protection of the primary alcohol, and oxidation with PCC on neutral alumina gave the methyl ketone **6**, without evidence of α-epimerization (83% yield from **4**). Nucleophilic addition of 3-butenylmagnesium bromide at −78 °C led exclusively to the tertiary alcohol **7**. Conversion to the butyrolactone was conveniently accomplished via ozonolysis of the terminal alkene,[8] producing an intermediate lactol for subsequent oxidation with pyridinium chlorochromate yielding lactone **8** (80% for the two steps). This transformation was also performed in a single step using cetyltrimethylammonium permanganate (CTAP),[9] yielding 75% of the desired butyrolactone **8**; however, the two-step procedure was more convenient for large-scale experiments. Desilation and oxidation of the primary alcohol **9** using PCC on neutral alumina afforded the sensitive α-alkoxy aldehyde **10** (δ 9.59 (d, C*H*O, J = 2.2 Hz)) in 88% yield (71% overall from **7**).[10] This aldehyde could not be stored and was used immediately for further chemistry.

Reactions of **10** with 3-lithiofuran as prepared by halogen–metal exchange of 3-bromofuran[11] using *n*-butyllithium led to poor yields of addition products.[12] However, the exchange was more cleanly accomplished by using *sec*-butyllithium (1 equiv) at −78 °C in anhydrous ether. Further addition of a solution of magnesium bromide etherate (1 equiv, Aldrich) gave a yellow-green solution, which was added dropwise via cannula to a solution of aldehyde **10** at −78 °C. This procedure offered excellent yields of the secondary alcohol **11** as a separable mixture of diastereoisomers (75:25 ratio). Oxidation to the ketone **12** was most readily achieved by using Swern conditions at −78 °C, since PCC was found to attack the furan ring and MnO_2 oxidations proceeded only very slowly. This ketone was also prone to undergo α-epimerization. However, isomerization was avoided by quenching oxidations at −20 °C with saturated aqueous ammonium chloride and immediate filtration through a pad of silica gel using ethyl acetate.[13]

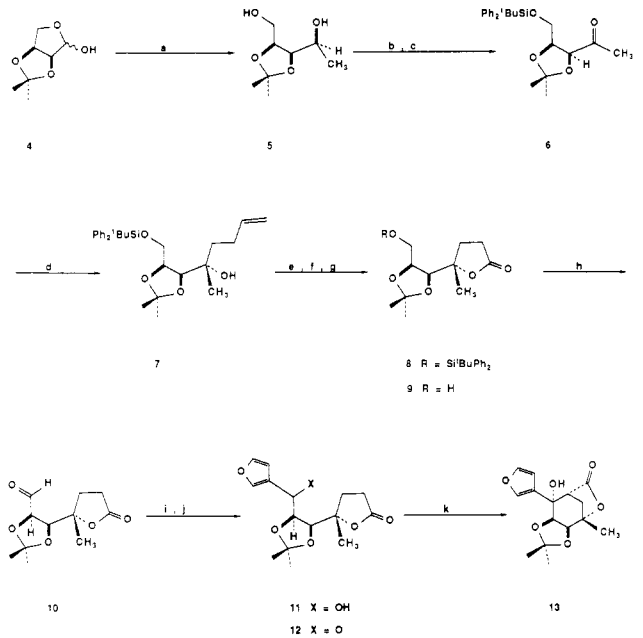
Our intramolecular Claisen condensations were conducted by inverse addition of a solution of LDA maintained at 0 °C, to a solution of keto ester **12** in anhydrous tetrahydrofuran at −78 °C.[14] Stereoselective formation of the desired bicyclic lactone **13** was obtained in yields ranging from 67% to 72% following silica gel chromatography, with additional amounts of the corresponding C-7 diastereomeric tertiary alcohol (ratio 80:20). Likewise, reactions of the C-4 diastereoisomeric lactone **14** produced **15** and **16** with similar efficiency and product ratios.[15] In either case, major products appear to be formed from the acyclic, chairlike arrangements **13a** and **15a**. Dreiding models suggest an unfavorable steric interaction of the furanyl substituent and the attacking enolate observed in the C_6–C_7 rotamers of **13a** and **15a**. However, it is difficult



to assess the importance of the synclinal relationship of the C-7 ketone and enolate. In contrast, intramolecular condensations involving the diastereomeric tetrahydrofuranones **17** and **18** gave complete stereocontrol, each affording a single isomer in 75–85% yields.[16] Assuming that the cis ring fusions of oxahydrindanes **19** and **20** are favored kinetically ($\Delta H^{\ddagger}$), only the corresponding con-

(7) Perlin, A. S. *Methods Carbohydr. Chem.* **1962**, *1*, 67.
(8) The intermediate ozonide is particularly stable and is only very slowly reduced by dimethyl sulfide.
(9) Rathore, R.; Vankar, P. S.; Chandrasekaran, S. *Tetrahedron Lett.* **1986**, *27*, 4079.
(10) Swern oxidation of **9** at −78 °C led to considerable isomerization. Storing the neat aldehyde **10** at 0 °C overnight produced 5–10% α-epimerization.
(11) Commercially available from Aldrich. Srogh, J.; Janda, M.; Stibor, I. *Collect. Czech. Chem. Commun.* **1970**, *35*, 3478.
(12) Fukuyama, Y.; Kawashima, Y.; Miwa, T.; Tokoroyama, T. *Synthesis* **1974**, 443.
(13) After this rapid workup, ketone **12** was purified via column chromatography on silica gel (40% ethyl acetate in hexanes) to provide 79% yield of a single isomer. The product may be stored for up to 24 h in the freezer without α-epimerization but was generally used immediately for conversion to **13**.
(14) Typically conditions for our intramolecular Claisen condensations are described as follows: keto ester (850 mg, 1.76 mmol) was dissolved in dry THF (4 mL) and cooled to −78 °C under argon. Dropwise addition of 5.6 mL (2.2 mmol) of a freshly prepared 0.4 M stock solution of lithium diisopropylamide (maintained at 0 °C) in THF led to completion of reactions within 10 min (as monitored by TLC). In some cases reactions were warmed to −60 °C prior to addition of LDA. After quenching with cold aqueous NH_4Cl solution, extraction with ethyl acetate gave an organic phase, which was washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography on silica gel using 30% ether in pentane (30% EtOAc in hexanes for some examples) gave 620 mg (73%) of product as a waxy solid. Yields were usually 10% greater on smaller scale runs (25–100 mg).
(15) Lactone **14** was prepared stereoselectively by reversing the order of methyl magnesium chloride and 3-butenylmagnesium bromide additions as shown in Scheme I. Partial characterization as follows. **13**: ^{1}H NMR (360 MHz, $CDCl_3$/TMS) δ 1.28 (s, 3 H), 1.30 (s, 3 H), 1.55 (s, 3 H), 2.06 (ddd, 1 H, J = 2.0 Hz, 6.0 Hz, J = 13.0 Hz), 2.64 (d, 1 H, J = 13.0 Hz), 3.06 (d, 1 H, J = 6.0 Hz), 4.30 (dd, 1 H, J = 2.0 Hz, J = 6.2 Hz), 4.50 (d, 1 H, J = 6.2 Hz), 6.47 (m, 1 H), 7.38 (m, 1 H), 7.45 (m, 1 H). **15**: ^{1}H NMR (360 MHz, $CDCl_3$/TMS) δ 1.42 (s, 3 H), 1.46 (s, 3 H), 1.62 (s, 3 H), 1.77 (d, 1 H, J = 13.0 Hz), 2.13 (dd, 1 H, J = 6.0 Hz, J = 13.0 Hz), 2.85 (dd, 1 H, J = 1.2 Hz, J = 6.0 Hz), 4.03 (d, 1 H, J = 5.5 Hz), 4.65 (dd, 1 H, J = 1.2 Hz, J = 5.5 Hz), 6.50 (m, 1 H), 7.48 (m, 2 H).
(16) Syntheses of ketones **17** and **18** and subsequent transformations in this series will be described elsewhere. Partial characterization as follows: **19**: ^{1}H NMR (300 MHz; $CDCl_3$/TMS) δ 1.10 (s, 9 H), 1.29 (ddd, 1 H, J = 1.0 Hz, J = 5.5 Hz J = 14.3 Hz), 1.32 (s, 3 H), 1.68 (d, 1 H, J = 14.3 Hz), 2.23 (d, 1 H, J = 5.5 Hz), 3.27 (dd, 1 H, J = 1.0 Hz, J = 6.0 Hz), 3.39 (s, 3 H), 3.88 (dd, 1 H, $J \approx$ 8.2 Hz, J = 8.8 Hz), 3.98 (dd, 1 H, J = 8.2 Hz, J = 8.8 Hz), 4.14 (d, 1 H, J = 6.0 Hz), 4.51 (dd, 1 H, J = 8.2 Hz, J = 8.8 Hz), 7.4–7.7 (m, 10 H). **20**: ^{1}H NMR (300 MHz; $CDCl_3$/TMS) δ 1.08 (s, 9 H), 1.50 (s, 3 H), 2.10 (dd, 1 H, J = 5.5 Hz, J = 12.5 Hz), 2.33 (dd, 1 H, J = 1.2 Hz, J = 5.5 Hz), 2.44 (d, 1 H, J = 12.5 Hz), 3.38 (dd, 1 H, J = 4.5 Hz, J = 10.5 Hz), 3.43 (d, 1 H, J = 4.7 Hz), 3.48 (s, 3 H), 3.89 (dd, 1 H, J = 6.2 Hz, J = 10.5 Hz), 4.02 (dd, 1 H, J = 1.5 Hz, J = 4.8 Hz), 4.43 (dd, 1 H, J = 4.5 Hz, J = 6.2 Hz), 7.4–7.7 (m, 10 H).

Scheme I[a]

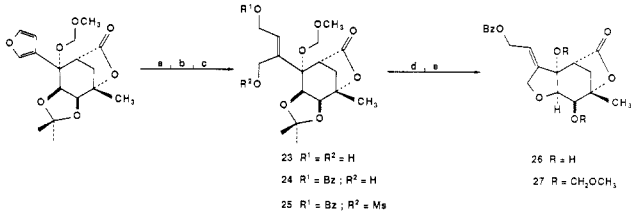


[a] (a) MeMgCl, THF, −78 °C (88%); (b) Ph_2-*t*-BuSiCl, DMF, imidazole, −30 °C (99%); (c) PCC on neutral Al_2O_3, CH_2Cl_2, 22 °C (95%); (d) $H_2C{=}CHCH_2CH_2MgBr$, THF, −78 °C (95%); (e) O_3, CH_2Cl_2, −78 °C, then Ph_3P (90%); (f) PCC on neutral Al_2O_3, CH_2Cl_2, 22 °C (89%); (g) Add 1.0 M *n*-$Bu_4N^+F^-$, THF, 0 °C (98%); (h) PCC on neutral Al_2O_3, CH_2Cl_2, 0.8 equiv of NaOAc, 22 °C (88%); (i) 3-bromofuran, 1.3 M *sec*-BuLi, Et_2O, −78 °C, then $MgBr_2{\cdot}Et_2O$ (0.9 equiv), −78 → −40 °C (87%); (j) ClCOCOCl, CH_2Cl_2, DMSO, −78 °C, then Et_3N, −78 → −20 °C (79%); (k) THF, −78 °C, then LDA (67%).

formers **21** and **22** provide a reasonable trajectory for the internal attack of the enolate, thus asserting stereocontrol at C-2. Remarkably, these condensations apparently occur without competing deprotonations adjacent to the ketone carbonyls of **12**, **14**, **17**, and **18**, we find no evidence of α-epimerization or β-alkoxy eliminations.[17]

Transformation of furan **13** into the hexahydrobenzofuran moiety of the milbemycin–avermectin antibiotics is demonstrated in Scheme II starting with protection of the tertiary alcohol of **13**.[18] Oxidation of the furan ring using *N*-bromosuccinimide in aqueous tetrahydrofuran at 0 °C followed by direct addition of sodium borohydride gave the desired 2-butene-1,4-diol **23** in 84% isolated yield. Selective benzoylation at **23** and subsequent reaction with methanesulfonyl chloride led to the unstable mesylate **25**. Treatment with an acidic ion-exchange resin (Dowex 50W-X8) at 70 °C provided the desired ring closure to the tetrahydrofuran **26** in excellent yield. Under these conditions the methoxymethyl ether at C-7 was also cleaved. Note that the same sequence of reactions as applied to the isomeric lactone **15** failed to produce ring closure of the tetrahydrofuranyl system.[19] Finally, X-ray diffraction

Scheme II[a]



[a] (a) NBS (1 equiv), H_2O–THF (1:4), 0 °C, then $NaBH_4$ (84%); (b) BzCl (1 equiv), CH_2Cl_2, Et_3N, catalytic 4-DMAP, −78 → −40 °C (82%); (c) H_3CSO_2Cl, CH_2Cl_2, Et_3N, 0 °C (90%); (d) THF–H_2O (1:1), Dowex 50W-X8, 70 °C (82%); (e) MOMCl (5 equiv), DMF, 0 °C, add NaH (81%).

studies of the bis(methoxymethyl) ether **27** (mp 75–76 °C; $[\alpha]^{26}_D$ +97.2° (*c* 0.54, $CHCl_3$)) unambiguously confirmed our stereochemical assignments,[20] and selective hydrolysis to the allylic alcohol **3** (LiOH, THF, aqueous MeOH, −20 °C) affords an appropriate key intermediate for further chemistry.[20] Similarly, crystallographic studies of the corresponding C-8 benzoate of **20** conclusively supported our structural elucidations in this series.[21]

In conclusion, our efforts have demonstrated a study of highly selective, intramolecular Claisen condensations of sensitive substrates under conditions of kinetic deprotonation, which affords a novel and efficient route to the hexahydrobenzofuran unit as required for synthesis of the milbemycin–avermectin antibiotics.

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Supplementary Material Available: A listing of data for characterization of key compounds, **6**, **7**, **9**, **10**, **12**, **13**, **23**, **26**, **27**, and X-ray diffraction data for **27** and the C-8 benzoate of **20**, including tables of fractional coordinates, thermal parameters, bond distances, and bond angles (19 pages). Ordering information is given on any current masthead page.

(17) Subsequent to submission of our manuscript, a related aldol strategy for construction of the chiral hexahydrobenzofuran component has also appeared. Hirama, M.; Noda, T.; Itô, S.; Kabuto, C. *J. Org. Chem.* **1988**, *53*, 706.

(18) It is essential to introduce MOMCl (2 equiv, DMF, 0 °C, 82% yield) into the reaction mixture prior to addition of sodium hydride. The usual order of addition provides 30% yields of the retroaldol process and subsequent decomposition products.

(19) Prolonged reactions of the corresponding diastereomeric mesylate from **15** with Dowex 50W-X8 gave the triol mesylate without ring closure, and similar treatment using trifluoroacetic acid led to acetonide migration affording the isomeric 6,7-*O*-isopropylidene derivative.

(20) Structure assignments of **27** are based on its single-crystal X-ray diffraction (−152 °C). All atoms were located and refined by full-matrix least-squares to final residuals of $R(F)$ = 0.074 and $R_w(F)$ = 0.067. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 87128. Partial characterization of **3**: ^1H NMR (360 MHz, $CDCl_3$/TMS) δ 1.49 (s, 3 H), 1.70 (br s, OH), 1.88 (ddd, 1 H, J = 1.1 Hz, J = 5.5 Hz, J = 12.3 Hz), 2.42 (d, 1 H, J = 12.3 Hz), 3.17 (d, 1 H, J = 5.5 Hz), 3.40 (s, 3 H), 3.48 (s, 3 H), 3.97 (dd, 1 H, J = 1.1 Hz, J = 5.9 Hz), 4.22 (d, 2 H, J = 5.7 Hz), 4.35 (d, 1 H, J = 5.9 Hz), 4.58 (dd, 1 H, J = 1.5 Hz, J = 13.3 Hz), 4.62 (d, 1 H, J = 6.6 Hz), 4.65 (d, 1 H, J = 7.6 Hz), 4.73 (d, 1 H, J = 13.3 Hz), 4.82 (d, 1 H, J = 7.6 Hz), 4.94 (d, 1 H, J = 6.6 Hz), 5.68 (m, 1 H).

(21) Structural elucidation of **20** was completed by an X-ray diffraction study of a rhombic crystal of the corresponding C_8 benzoate of **20** (−155 °C). All atoms were located and refined by full-matrix least-squares to final residuals of $R(F)$ = 0.045 and $R_w(F)$ = 0.044. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 87066.

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