Irreducible Analogues of Mevaldic Acid Coenzyme A Hemithioacetal as Potential Inhibitors of HMG-CoA Reudctase. 2. Synthesis of a Secondary Alcohol Analogue of Mevaldic Acid Pantetheine Hemithioacetal and an Amide Analogue of 3-Hydroxy-3-methylglutaryl-*S*-pantetheine

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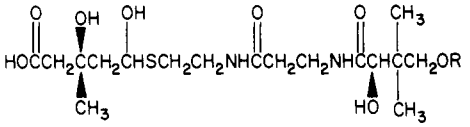
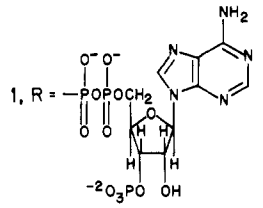
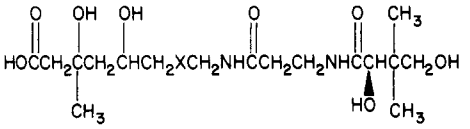
Syntheses of *erythro*-**3b**, *threo*-**3b**, and **4**, which are irreducible analogues of mevaldic acid coenzyme A hemithioacetal, **1**, and mevaldic acid pantetheine hemithioacetal, **2**, are described. Synthesis of **4** required conversion of the acetal ester **8** to **7** with ethylenediamine followed by coupling of **7** with pantothenic acid, **6**, to give **9**. The acetal in **9** was hydrolyzed to provide **10**, oxidation of which completed the synthesis. Preparation of the two diastereomers of **3b** began with ozonization of **11** to give aldehyde ester **12** which was in turn converted to the triol **14** by treatment with the Grignard reagent **13**. Hydrolysis of **14** followed by lactonization provided **16**. The primary alcohol in **16** was converted, via the tosylate **17** and the azide **18**, to the amine **19**. Coupling **19** with **6** provided the cis and trans lactones **21** which could be separated by HPLC and hydrolyzed to *threo*- and *erythro*-**3b**, respectively. The products, which were initially designed as inhibitors, are being examined as probes of the enzyme HMG-CoA reductase for which **1** is postulated to be a strongly enzyme-bound intermediate.

We have postulated[1,2] that analogues of mevaldic acid coenzyme A hemithioacetal, **1**, which cannot be further reduced to mevalonic acid because they lack the labile C–S bond in **1**, should act as inhibitors of the enzyme HMG-CoA reductase, the key regulated enzyme in sterol biosynthesis. This postulate has led us to initiate a synthetic program to prepare such compounds. For reasons detailed in the previous paper of this series,[1] the target structures initially chosen were analogues of mevaldic acid *S*-pantetheine **2** having the general structure **3**. In our previous





2, R = H

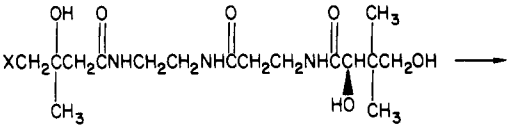


3a, X = S
3b, X = CH_2

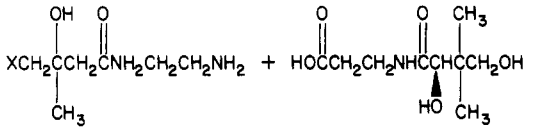
report we have described the synthesis of **3a** in which the sulfur atom and the adjacent methylene group in **2** have been interchanged to give a secondary alcohol in place of the hemithioacetal in **2**. In this report we describe preparation of two structures: **3b** in which the sulfur atom in **1b** has been replaced by a methylene group and **4** in which the entire hemithioacetal functionality has been replaced by an amide. (This latter structure was envisioned as deriving its similarity with **2** from the interaction of the amide nitrogen with the carbonyl group leading to significant C–O single bond character.)

Results and Discussion

The construction of **4** was viewed as arising from coupling a primary amine similar to **5**, which includes an appropriately protected form of the 3-hydroxy-3-methylglutaryl moiety, with pantothenic acid (**6**). Since the latter component is available in the form of calcium pantothenate, the synthesis reduces to preparing the amine and coupling it with **6**.

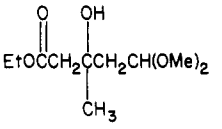


4, X = HOOC
9, X = $(MeO)_2CH$
10, X = HC(O)



5, X = HOC(O)
7, X = $(MeO)_2CH$

6



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(1) Fischer, G. C.; Turakhia, R. H.; Morrow, C. J. *J. Org. Chem.* **1985**, *50*, 2011.

(2) In our previous paper,[1] we neglected to mention reports by Eggerer and co-workers[3,4] describing inhibitors of HMG-CoA reductase that are analogues of **1**[3] and **2**[4] in which the hydroxyl group of the hemiacetal has been replaced by a hydrogen to give a sulfide in each case. They also report[4] that the thio esters 3-hydroxy-3-methylglutaryl-*S*-pantetheine and -*S*-phosphopantetheine are substrates for HMG-CoA reductase in contrast to an earlier report[5] that the former is not a substrate for this enzyme. We appreciate Professor Eggerer calling these reports to our attention and apologize for the oversight.

(3) Nguyen, T.-G.; Aigner, H.; Eggerer, H. *FEBS Lett.* **1981**, *128*, 145.

(4) Nguyen, T.-G.; Gerbing, K.; Eggerer, H. *Hoppe-Seyler's Z. Physiol. Chem.* **1984**, *365*, 1.

(5) Rêtey, J.; von Stetten, E.; Coy, U.; Lynen, F. *Eur. J. Biochem.* **1970**, *15*, 72.

† Taken in part from the Ph.D. dissertation of R.H.T., University of New Mexico, 1983.

‡ National Science Foundation Undergraduate Research Participant, 1979.

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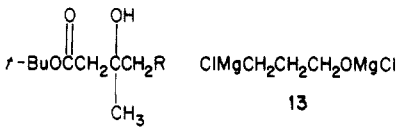
We chose to explore use of the acetal **7** since the coupling of **7** with **6** would provide a useful model for a corresponding step in one of the anticipated routes to **3b**. The required **7** was prepared in 60% yield by heating racemic ethyl 3-hydroxy-5,5-dimethoxy-3-methylpentanoate, **8**,[6] with excess ethylenediamine. Pantothenic acid (**6**) could be prepared from the hemicalcium salt in about 75% yield either by treatment of the salt with aqueous oxalic acid or by use of an acidic cation exchange resin.

Formation of the amide linkage between **7** and **6** to give **9** was effected in 70% yield by the method of Mukaiyama and co-workers[8] using triphenylphosphine and 2,2′-dipyridyl disulfide in DMF solution. Hydrolysis of **9** in 0.1 N H_2SO_4 provided aldehyde **10** in 84% yield. The crude aldehyde was immediately treated with freshly prepared silver oxide[9] to give the desired **4** in 85% yield.

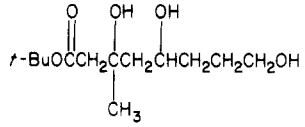
The pantetheine mevaldic acid analogue **3b** proved to be the most difficult synthetic target among those prepared to date. The many sequences explored in the course of synthesizing this compound are discussed elsewhere.[10]

The successful route began with ozonization of racemic *tert*-butyl 3-hydroxy-3-methyl-5-hexenoate, **11**,[11] followed by workup with dimethyl sulfide[12] to provide *tert*-butyl 3-hydroxy-3-methyl-5-oxopentanoate, **12**, in 76% yield.



11, R = CH=CH$_2$
12, R = CHO

13



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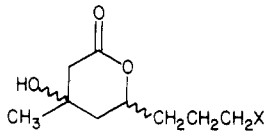
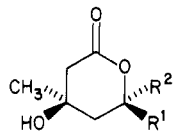


15, X = OC(O)H
16, X = OH
17, X = OTs
18, X = N_3
19, X = NH_2

Aldehyde **26** was allowed to react with an excess of Grignard reagent **13**,[13] to provide the trihydroxy ester **14** in 70% yield. Formic acid converted **14** to lactone formate **15** which could be hydrolyzed to diol lactone **16** in 51% overall yield. Alternatively, **14** could be converted to **16** in 62% yield by alkaline hydrolysis of the *tert*-butyl ester followed by acidification of the reaction mixture.

Further elaboration of **16** to the amino lactone **19** was effected by selective reaction of the primary hydroxyl in **16** with toluenesulfonyl chloride to give the lactone tosylate **17** in 66% yield. The tosylate was then displaced with an azido group by treating **17** with sodium azide in DMF to give **18** in 70% yield. Hydrogenation of **18** over platinium oxide provided the amino lactone **19** as an unstable material that had to be carried on to the subsequent product after partial characterization.

Compounds **14–19** are, of course, formed as mixtures of diastereomers. Since both diastereomers of **3b** relative to carbons 3 and 5 were desired, no attempt was made to control the stereochemistry of the synthesis in anticipation of separating the stereoisomers at an optimal point in the synthetic scheme. It was found that such a separation could be readily effected during the HPLC purification of **18**. The stereochemistries of the resulting *cis*- and *trans*-**18**[14] were assigned on the basis of the chemical shift of the proton on the δ-carbon in the ^{1}H NMR spectrum of each stereoisomer by analogy with the assignments made by Shimada and co-workers[15] for the compounds *cis*- and *trans*-**20**. These workers found that the proton at carbon



cis-**20**, R^1 = CH_2CH_2Ph; R^2 = H
trans-**20**, R^1 = H; R^2 = CH_2CH_2Ph
cis-**18**, R^1 = $(CH_2)_3N_3$; R^2 = H
trans-**18**, R^1 = H; R^2 = $(CH_2)_3N_3$
cis-**21**, R^1 = $CH_2CH_2CH_2NHC(O)CH_2CH_2NHC(O)CH(OH)C(CH_3)_2CH_2OH$; R^2 = H
trans-**21**, R^1 = H; R^2 = $CH_2CH_2CH_2NHC(O)CH_2CH_2NHC(O)CH(OH)C(CH_3)_2CH_2OH$

6 appears 0.5 ppm further down field in the trans compound (δ 4.73) relative to the cis compound (δ 4.23). Thus, the azide displaying a one-proton multiplet at δ 4.71 in the ^{1}H NMR spectrum and eluting first in normal phase HPLC analysis was assigned the trans configuration while the azide displaying the multiplet at δ 4.23 was assigned the cis configuration.

Following hydrogenation of *trans*-**18** over PtO_2, a DMF solution of the resulting trans stereoisomer of amino lactone **19** was allowed to react with pantothenic acid in the presence of 2,2′-dipyridyl disulfide and triphenylphosphine.[8] Isolation of the coupling product **21** was achieved by using reverse-phase HPLC. While the ^{1}H and ^{13}C NMR spectra were consistent with structure **21**, they also indicated the presence of a few percent of a material that had the spectral characteristics of 2-pyridinethione (2-mercaptopyridine), an expected product of the coupling reaction. However, the aromatic impurity may well have been covalently bound to the product as attempts to remove it by extraction and by chromatography were unsuccessful.

To avoid this problem the coupling system was changed to *N*,*N*′-dicyclohexylcarbodiimide/*N*-hydroxysuccinimide (DCC/HOSU).[16] Using this pair of reagents, *cis*- and *trans*-**21** were prepared in low yield from *cis*- and *trans*-**19**, respectively. Alternatively, a stereoisomeric mixture of the two products could be prepared from *cis*/*trans*-**19**. The cis and trans lactones **21** were then separated by preparative reverse-phase HPLC.

Hydrolysis of the lactone in *cis*- and *trans*-**21** by allowing each to stir in pH 10 $Na_2CO_3/NaHCO_3$ buffer solution for 6 h[1] provided an aqueous solution of the target compounds *threo*- and *erythro*-**3b**, respectively, as salts eluting at the solvent front by HPLC. Each reverted to the corre-

(6) Wilson, W. K.; Baca, S. B.; Barber, Y. J.; Scallen, T. J.; Morrow, C. J. *J. Org. Chem.* **1983**, *48*, 3960. This compound was originally prepared via the Reformatsky reaction[7a] and has been prepared via a lithium enolate by using lithium amide.[7b]

(7) (a) Eggerer, H.; Lynen, F. *Justus Liebigs Ann. Chem.* **1957**, *608*, 71. (b) Pichot, L.; Blagoev, B.; Hardouin, J.-C.; *Bull. Soc. Chim. Fr.* **1968**, 4489.

(8) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1904.

(9) Campaigne, E.; LeSuer, W. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 919. Pearl, I. *Organic Syntheses*; Wiley: New York, 1963, Collect. Vol. IV, p 972.

(10) Turakhia, R. H. Ph.D. Dissertation, 1983.

(11) Tschesche, R.; Machleidt, H. *Justus Liebigs Ann. Chem.* **1960**, *631*, 61.

(12) Pappas, J. J.; Keaveny, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

(13) Godleski, S. A.; Valpey, R. S. *J. Org. Chem.* **1982**, *47*, 381.

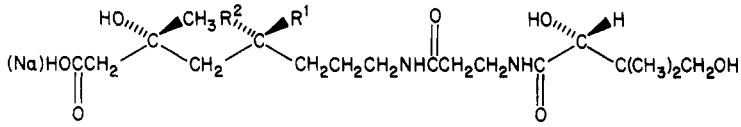
(14) The designations cis and trans refer to the relationship between the hydroxyl group at position 4 and the alkyl group at position 6 in structures **18–21**.

(15) Sato, A.; Ogiso, A.; Nogushi, H.; Mitsui, S.; Kareko, I.; Shimada, Y. *Chem. Pharm. Bull.* **1980**, *24*, 1509.

(16) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1934.

sponding stereoisomer of **21** upon acification of the solution in an attempt to isolate the *threo-* or *erythro-***3b**.

It should be noted that *cis-* and *trans-***21** as well as *threo-* and *erythro-***3b** are actually mixtures of diastereomeric pairs. They are antipodes at two chiral centers but identical at the third because they were prepared from optically active pantothenic acid. None of the separation methods examined was able to distinguish these pairs of diastereomers. However, methods are being developed[6] to permit chiral synthesis of compounds such as those described here.



threo-**3b**, R^1=OH, R^2=H
erythro-**3b**, R^1=H, R^2=OH

Compound **4**, the individual diasteromers of lactone **21**, and the aqueous solutions of carboxylates **3b** were tested for inhibition of rat liver microsomal HMG-CoA reductase and found to be only weak inactivators of the enzyme in the assay used. Details of these studies will be reported elsewhere. Currently, we are endeavoring to extend the syntheses reported here to give an irreducible analogue of the entire mevaldic acid coenzyme A hemithioacetal molecule **1** as well as its ketone precursor which should behave as a partially reducible analogue of HMG-CoA itself.

Experimental Section

General Experimental Methods and Instrumentation General Methods. Elemental analyses were performed at the University of New Mexico microanalytical laboratory. All procedures described were performed in a nitrogen atmosphere. Procedures requiring anhydrous conditions were performed in an oven-dried apparatus cooled under dry nitrogen. Magnesium sulfate was used to dry organic extracts. Solvents were removed via a rotary evaporator or on a Kugelrohr apparatus. Ozone for ozonolysis reactions was produced as a solution in pure oxygen by using an ozonator from PCI Ozone Corporation. Reactions were stirred magnetically unless otherwise indicated. Column chromatography was performed on silica Gel 60 (EM Reagents, 230–400 mesh) as the stationary phase. Analytical thin-layer chromatography (TLC) was carried out with glass-backed silica gel plates (Fisher Scientific Co.) or polyethylene-backed silica gel plates with fluorescent indicator (Eastman). Visualization was achieved with either 10% ethanolic phosphomolybdic acid (glass-backed plates) or UV radiation (polyethylene-backed plates).

Materials. Organic reagents were purchased from Aldrich Chemical Co. unless otherwise indicated. Solvents and commercially available starting materials were generally used without additional purification. Where anhydrous conditions were necessary, either Aldrich Gold Label anhydrous solvents were used or high grade solvents were dried according to standard procedures.

Instrumentation. ^{1}H NMR spectra were recorded on either a Varian EM-360 spectrometer or a Varian FT-80A NMR spectrometer. Chemical shifts are reported as ppm (δ) downfield from Me_4Si (or DSS for D_2O solutions) which was used as an internal standard. ^{13}C NMR spectra were recorded on the Varian FT-80A spectrometer. Chemical shifts are reported as ppm (δc) with respect to Me_4Si as determined from (1) $CDCl_3$ assuming a chemical shift of 76.9 ppm for $CDCl_3$, (2) Me_2SO-d_6 assuming a chemical shift of 39.6 ppm for Me_2SO-d_6, or (3) *p*-dioxane assuming a chemical shift of 67.4 ppm for *p*-dioxane in D_2O. Infrared spectra were recorded on a Perkin-Elmer 237B or 337 IR spectrophotometer and were referenced to the 1601 and/or 1030 cm^{-1} polystyrene bands. High performance liquid chromatography (HPLC) analyses were performed by employing a Waters Associates 6000A pump, a U6K injector, and a RCM 100 radial compression module. A Waters Associates R401 differential refractometer and/or a sequential Schoeffel 770 UV detector were used. A μ-Porosil normal-phase column (8 mm i.d. × 10 cm) was used with hexanes/ethyl acetate mixtures as the mobile phase while a μ-Bondapak C_{18} reverse-phase column was used with water/methanol mixtures as the mobile phase. Preparative HPLC was carried out with a Waters Associate Prep LC/System 500 using a Prep PAK-500/silica cartridge with hexanes/ethyl acetate mixtures as the mobile phase or a Prep PAK-500/C_{18} cartridge with methanol/water mixtures as the mobile phase. Gas–liquid chromatography (GLC) analyses were performed on a Varian 3700 gas chromatograph using helium as the carrier gas and either a 10% QF-1, 6 ft × $^1/_4$ in. or a 5% SE-30, 6 ft × $^1/_8$ in. stainless steel packed column.

Ethyl 3-hydroxy-5,5-dimethoxy-3-methylpentanoate (8) was synthesized according to the procedure of Cane and Levin[17] and characterized by ^{1}H and ^{13}C NMR.

***N*-(2-Aminoethyl)-3-hydroxy-5,5-dimethoxy-3-methylpentanamide (7)** was prepared by using the general procedure of Baganz et al.[18] by adding 5.00 g (22.7 mmol) of ethyl 3-hydroxy-5,5-dimethoxy-3-methylpentanoate, 8,[6] dropwise to 8.17 g (136.2 mmol) of ethylenediamine. The reaction mixture was then refluxed at 125 °C in an oil bath for 40 h. Ethylenediamine was removed in vacuo and the oil obtained was dissolved in 50 mL of water. The aqueous layer was washed with ether (3 × 30 mL) and the water removed by freeze-drying. The oily residue was then dissolved in chloroform, the solution dried, and the solvent removed in vacuo to obtain 3.61 g (68%) of **7** as a light brown oil: ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1 H, -NH-), 4.64 (t, 1 H, 1-H), 3.23 (s, 1 H, 3-OH), 3.32 (s, 8 H, 1-OCH_3 and -NH_2), 3.03 and 2.67 (m, 4 H, 6-H and 7-H), 2.39 (s, 2 H, 4-H), 1.84 (d, 2 H, 2-H), 1.25 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$) δ 171.60 (C-5), 101.73 (C-1), 69.02 (C-3), 52.18 (1-OCH_3), 46.60 and 43.35 (C-2 and C-4), 41.36 and 40.68 (C-6 and C-7), 26.80 (3-CH_3). Anal. Calcd for $C_{10}H_{22}N_2O_4$: C, 51.26; H, 9.47; N, 11.95. Found: C, 50.83; H, 9.47; N, 12.10.

3-[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanoic Acid (Pantothenic Acid) (6). Method A. A mixture of 1.00 g (2.10 mmol) calcium pantothenate [Sigma Chemical Co.] dissolved in 10 mL of water and 0.19 g (2.10 mmol) of oxalic acid dissolved in 5 mL of water was stirred overnight at room temperature. The fine precipitate was removed by centrifuging the reaction mixture and then the water was removed by freeze-drying. The oil obtained was dissolved in methanol, the solution dried, and the solvent removed in vacuo to obtain 0.75 g (81%) of **6** as a colorless viscous oil.

Method B. A chromatographic column 2.5 cm in diameter was filled with Dowex 50W-X8 ion exchange (140 mequiv, wet capacity 1.9 mequiv/mL) suspended in water. A solution of 10.00 g (21 mmol) of calcium pantothenate dissolved in 30 mL of water was then passed slowly through the column. By eluting with water, 200 mL of a solution of pantothenic acid was obtained. The water was removed by freeze-drying, the resulting oil dissolved in methanol, the solution dried, and the solvent removed in vacuo to afford 6.70 g (72%) of **6** as a colorless viscous oil. The product obtained with both methods was identical: ^{1}H NMR (D_2O) δ 3.88 (s, 1 H, 5-H), 3.33 (m, 4 H, 3-H and 7-H), 2.55 (t, 2 H, 2-H), 0.82 (s, 6 H, 6-CH_3); ^{13}C NMR (D_2O) δ 176.70 and 175.69 (C-1 and C-4), 76.81 (C-5), 69.39 (C-7), 39.44 (C-3), 35.58 and 34.44 (C-2 and C-6), 21.26 and 20.12 (6-CH_3).

***N*-[3-[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanamido]ethyl]-3-hydroxy-5,5-dimethoxy-3-methylpentanamide, diastereomer mixture (9)** was prepared according to the general procedure of Mukaiyama et al.[8] A mixture of 2.40 g (10.2 mmol) amine **7** and 2.10 g (8.5 mmol) of triphenylphosphine in 25 mL of DMF was added dropwise to a mixture of 1.71 g (8.5 mmol) of pantothenic acid (**6**) and 1.76 g (8.5 mmol) of 2,2′-dipyridyl disulfide in 25 mL of DMF. The reaction mixture was stirred for 1 h under N_2 and then the solvent was removed in vacuo and the solid residue was sonicated sequentially with ether (3 × 30 mL), benzene (3 × 30 mL), and chloroform (3 × 250 mL). The residue was dried in vacuo to obtain 2.60 g (71%) of **9** as a pale yellow solid: ^{1}H NMR (D_2O) δ 4.86–4.62 (m, 1 H, 1-H), 3.92 (s, 1 H, 12-H), 3.63–2.91 (m, 14 H, 1-OCH_3, 6-H, 7-H, 10-H, and

(17) Cane, D. E.; Levin, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 1183.
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14-H), 2.63–2.32 (m, 4 H, 4-H and 9-H), 1.87 (d, 2 H, 2-H), 1.25 (s, 3 H, 3-CH_3), 0.84 (s, 6 H, 13-H); ^{13}C NMR (D_2O) δ 175.63, 174.64, and 174.24 (C-5, C-8, and C-11), 103.48 (C-1), 76.83 (C-12), 71.03 (C-3), 69.38 (C-14), 54.22 (1-OCH_3), 48.09 and 44.65 (C-2 and C-4), 39.57, 39.37, and 39.24 (C-6, C-7, and C-10), 36.19 and 34.14 (C-9 and C-13), 27.09 (3-CH_3), 21.34 and 20.07 (13-CH_3). Anal. Calcd for $C_{19}H_{37}N_3O_8$: C, 52.40; H, 8.56; N, 9.65. Found: C, 52.14; H, 8.51; N, 9.58.

***N*-[3-[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]-propanamido]ethyl]-3-hydroxy-3-methyl-5-oxopentanamide, Diastereomer Mixture (10).** To a solution of 0.20 g (0.46 mmol) of **9** dissolved in 15 mL of water was added 15 mL of 0.1 N H_2SO_4. The reaction mixture was stirred for 8 h and then was neutralized with sodium bicarbonate solution to pH 7 and freeze-dried to remove water. The resulting solid was dissolved in methanol and filtered to remove inorganic salts, the solution dried, and the solvent evaporated in vacuo to obtain 0.15 g (84%) of **10** as a solid. The crude product was used directly in the next step without purification: ^1H NMR (D_2O) δ 4.0 (s, 1 H, 12-H), 3.90–3.30 (m, 9 H, 1-H, 6-H, 7-H, 10-H, and 14-H), 2.69–2.05 (m, 6 H, 2-H, 4-H, and 9-H), 1.28 (s, 3 H, 3-CH_3), 0.92 (s, 6 H, 13-CH_3); ^{13}C NMR (D_2O) δ 175.60, 174.69, and 174.62 (C-5, C-8, and C-11), 76.79 (C-12), 71.04 (C-3), 69.39 (C-14), 48.05 and 44.62 (C-2 and C-4), 39.50, 39.36, and 39.26 (C-6, C-7, and C-10), 36.98 and 36.18 (C-9 and C-13), 27.13 (3-CH_3), 21.38 and 20.27 (13-CH_3).

4-[[3-[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]-propanamido]ethyl]carbamoyl]-3-hydroxy-3-methylbutanoic acid, diastereomer mixture (4) was prepared according to the general procedure of Pearl et al.[9] Silver oxide was freshly prepared by adding a solution of 0.41 g (2.4 mmol) of silver nitrate dissolved in 100 mL of water to a solution of 0.17 g (4.8 mmol) of sodium hydroxide in 100 mL of water. Continuous shaking during the addition ensured completion of the reaction and resulted in a brown semisolid mixture. The silver oxide was filtered off and washed with cold water and then was transfered to a 500-mL round-bottomed flask, covered with 100 mL of water, and treated with 0.48 g (12 mmol) of sodium hydroxide with vigorous stirring. The resulting mixture was cooled in an ice bath and 0.50 g (2.4 mmol) of aldehyde **10** was added in small portions with stirring. The oxidation was complete within 15 min. The black silver suspension was removed by suction filtration and washed several times with portions of hot water. The ice chilled filtrate was acidified with dilute HCl to pH 4. The resulting solution was freeze-dried and the solid obtained was dissolved in methanol, filtered to remove insoluble inorganic salts, and dried, and the solvent was removed in vacuo to obtain 0.45 g (85%) of **4** as light yellow solid. An analytically pure sample was prepared by HPLC (C_{18} cartridge, 90% water/10% methanol, R_v 6 mL): ^1H NMR (D_2O) δ 4.09 (s, 1 H, 12-H), 3.98–3.27 (m, 8 H, 6-H, 7-H, 10-H, and 14-H), 2.90–2.18 (m, 6 H, 2-H, 4-H, and 9-H), 1.42 (s, 3 H, 3-CH_3), 0.96 (s, 6 H, 13-CH_3); ^{13}C NMR (D_2O) δ 175.45, 174.39, 172.62, and 171.62 (C-1, C-5, C-8, and C-11), 76.77 (C-12), 70.96 (C-3), 69.37 (C-14), 48.04 and 44.68 (C-2 and C-4), 39.54, 39.46, 39.21 (C-6, C-7, and C-10), 37.56 and 36.19 (C-9 and C-13), 27.22 (3-CH_3), 21.39 and 20.32 (13-CH_3). Anal. Calcd for $C_{17}H_{31}N_3O_8$: C, 50.36; H, 7.71; N, 10.36. Found: C, 50.01; H, 7.68; N, 10.24.

***tert*-Butyl 3-hydroxy-3-methyl-5-hexenoate (11)** was prepared according to the procedure of Tschesche et al.[11] as modified by Fischer et al.[1] and characterized by ^1H and ^{13}C NMR.

***tert*-Butyl 3-hydroxy-3-methyl-5-oxopentanoate (12)** was prepared by the general procedure of Pappas et al.[12] A solution of 10.00 g (50 mmol) of *tert*-butyl 3-hydroxy-3-methyl-5-hexenoate (**11**) in 75 mL of methanol was cooled to −20 °C in an ozonolysis tube. Ozonized oxygen gas was bubbled through the tube at a rate of 1 mmol/min for 90 min. While at −70 °C, the solution was flushed with N_2 and 8 mL (109 mmol) of dimethyl sulfide was added. The solution was stirred at −10 °C for 1 h, at 0 °C for 1 h, and at room temperature for 1 h. The solvent was then removed in vacuo and the residue was extracted with water and methylene chloride. The methylene chloride layer was washed with water (5 × 25 mL) and dried, and the solvent was removed in vacuo to yield 7.62 g (76%) of **12** as a colorless viscous oil. The crude product was used in the next step without further purification; GC (QF-1, 150 °C, 30 cc/min) t_R 8.8 min; ^1H NMR ($CDCl_3$) δ 9.92 (t, 1 H, 5-H), 3.53 (s, 1 H, 3-OH), 2.60 (m, 4 H, 2-H and 4-H), 1.46 (s, 6H, C(CH_3)$_3$), 1.36 (s, 3-CH_3); ^{13}C NMR ($CDCl_3$) δ 201.30 (C-5), 170.78 (C-1), 80.52 (*C*(CH_3)$_3$), 69.65 (C-3), 53.54 (C-4), 46.20 (C-2), 27.62 (C(*C*H_3)$_3$), 29.18 (3-CH_3).

***tert*-Butyl 3,5,8-Trihydroxy-3-methyloctanoate, Diastereomer Mixture (14).**[13] In a 1-L, three-necked, flask equipped with a mechanical stirrer, low temperature thermometer, and an addition funnel was placed 16.54 g (175 mmol) of 3-chloro-1-propanol and 270 mL of dry THF. The solution was then cooled to −20 °C. To this was added dropwise 87.5 mL (175 mmol) of 2 M methylmagnesium chloride in THF. Following the addition, the reaction mixture was kept at −20 °C for 20 min and then 0.65 g (3.5 mmol) of 1,2-dibromoethane and 6.40 g (262 mmol) of magnesium turnings were added and the resulting suspension was refluxed for 1 h. A further 0.65 g (3.5 mmol) of 1,2-dibromoethane was added to the suspension and the mixture was refluxed for an additional 2 h. A solution of 7.04 g (35 mmol) of aldehyde **12** in 100 mL of THF was then added at room temperature with constant stirring. Following the addition, the mixture was stirred for 2 h and then the complex was decomposed with 100 mL of saturated ammonium chloride solution. The aqueous layer was extracted with ether (4 × 25 mL) and the combined organic layers were washed with saturated sodium chloride solution and dried and the solvent was removed in vacuo to obtain 7.8 g (86%) of **14** as a light brown oil. An analytical sample was obtained by column chromatography with 100% ethyl acetate followed by 100% 2-propanol: TLC (silica gel, 100% ethyl acetate) R_f 0.14; ^1H NMR ($CDCl_3$) δ 3.91 (m, 1 H, 5-H), 3.82 (m, 5 H, 3-OH, 5-OH, 8-H, and 8-OH), 2.58 (d, 2 H, 4-H), 2.42 (s, 2 H, 2-H), 1.75–1.51 (m, 4 H, 6-H and 7-H), 1.48 (s, 9 H, C(CH_3)$_3$), 1.31 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$) δ 171.85 and 171.63 (C-1), 81.21 (*C*(CH_3)$_3$), 71.93 (C-3), 68.56 and 68.36 (C-5), 62.33 and 62.20 (C-8), 47.73, 46.44, and 44.95 (C-2 and C-4), 35.06 (C-6), 28.68 and 28.52 (C-7), 27.86 (C(*C*H_3)$_3$), 25.59 (3-CH_3). Anal. Calcd for $C_{13}H_{26}O_5$: C, 59.51; H, 10.00. Found: C, 59.40; C, 9.79.

4-Hydroxy-6-(3-hydroxypropyl)-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one, Diasteromer Mixture (16). Method A.[11] To a solution of 8.00 g (31 mmol) of crude triol **14** in 75 mL of methanol was added a solution of 10.00 g of potassium hydroxide in 75 mL of water. Following reflux for 6 h the mixture stood overnight at room temperature. Methanol was removed by rotary evaporation and then the solution was acidified with 6 N H_2SO_4 to pH 2 and stirred for 5 h. Extraction with methylene chloride (3 × 25 mL) removed nonpolar organic impurities. The aqueous layer was then saturated with solid sodium chloride, and the solution was continuously extracted with methylene chloride for 3 days to afford 3.60 g (62%) of **16** as a pale yellow oil.

Method B.[19] Triol **14** (0.50 g, 1.90 mmol) was dissolved in 10 mL of formic acid, and the mixture was stirred for 4 h. Evaporation of the solvent in vacuo afforded a brown oil, which was dissolved in chloroform, allowed to stir for 2 h in the presence of solid K_2CO_3, and filtered. The solvent was removed in vacuo to obtain 0.20 g of formylated lactone **15** which was dissolved in 60 mL of methanol and mixed with a solution of 1.61 g of $KHCO_3$ in 32 mL of water, and the combination was stirred for 4 days. Methanol was removed in vacuo, followed by freeze-drying to remove the water. To the solid residue was added 2-propanol and the mixture was filtered to remove insoluble inorganic salts. Evaporation of the solvent in vacuo provided 0.18 g (51%) of **16** as a brown oil. Both methods gave identical products: analytical HPLC (80% water/20% methanol, 2 cc/min) R_v 6.2 mL and 7.6 mL; IR (neat) 3400 (ROH), 1730 -C(O)O cm^{-1}; ^1H NMR (D_2O) δ 4.49 (m, 1 H, 6-H), 3.66 (s, 2 H, 9-H), 2.70 (s, 2 H, 3-H), 2.25–1.30 (m, 6 H, 5-H, 7-H, and 8-H), 1.41 (s, 3 H, 4-CH_3); ^{13}C NMR (D_2O) δ 175.87 and 175.25 (C-2), 79.22 and 79.00 (C-6), 69.39 and 68.59 (C-4), 62.54 and 62.09 (C-9), 44.75, 43.85, 42.89, and 40.89 (C-3 and C-5), 32.35 and 32.01 (C-7), 29.81 and 27.93 (C-8), 27.86 (4-CH_3). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.10; H, 8.61.

4-Hydroxy-4-methyl-6-(3-(tosyloxy)propyl)-3,4,5,6-tetrahydro-2*H*-pyran-2-one, diasteromer mixture (17) was prepared according to the general procedure of Spencer et al.[20] To a room temperature solution of 5.00 g (26 mmol) of diol **16** in 25

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mL of pyridine and 25 mL of methylene chloride was added a solution of 14.8 g (78 mmol) of freshly recrystallized *p*-toluenesulfonyl chloride in 25 mL of methylene chloride. The mixture was stirred overnight and then was poured into 50 mL of ice–water, the phases were separated, and the aqueous phase was extracted with methylene cloride (4 × 25 mL). The combined extracts were dried, and the solvent was removed in vacuo to obtain 5.70 g (66%) of **17** as a light brown oil: analytical HPLC (50% hexanes/50% ethyl acetate containing 1% 2-propanol, 2 cc/min) R_v 25.6 mL and 32.2 mL; IR (neat) 3425 (ROH), 1725 (-C(O)O-), 820 (-Ar-) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (q, 4 H, Ar-H), 4.04 (m, 2 H, 6-H and 4-OH), 3.50 (m, 2 H, 9-H), 2.54 (s, 2 H, 3-H), 2.44 (s, 3 H, ArCH_3), 1.70 (m, 2 H, 5-H), 1.33 (m, 4 H, 7-H and 8-H), 1.24 (s, 3 H, 4-CH_3); ^{13}C NMR ($CDCl_3$) 171.12 and 170.87 (C-2), 144.84, 132.73, 129.84, and 127.59 (C-Ar), 76.17 (C-6), 70.19 and 70.05 (C-4), 68.16 and 67.49 (C-9), 44.66, 43.87, 42.80, and 41.16 (C-3 and C-5), 31.25 (C-7), 29.60 and 28.82 (C-8), 24.43 (4-CH_3), 21.29 (ArCH_3). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.81; H, 7.13.

6-(3-Azidopropyl)-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one, diastereomer mixture (18) was prepared according to the general procedure of Bose et al.[21] To a solution of 5.25 g (15.35 mmol) of tosylate **17** in 50 mL of DMF was added a solution of 2.00 g (30.7 mmol) of sodium azide [Sigma Chemical Co.] in 6 mL of water. The mixture was heated at 80 °C for 8 h and then was stirred overnight at room temperature. The solvent was removed in vacuo and the residual solid was treated with 50 mL of water and 50 mL of methylene chloride. The phases were separated and the aqueous phase was extracted with methylene chloride (4 × 30 mL). The combined organic phases were dried, and the solvent was removed in vacuo to obtain 2.30 g (70%) of **18** as a light brown oil: analytical HPLC (55% hexanes/45% ethyl acetate containing 1% 2-propanol, 2 cc/min) R_v 20.6 mL and 25.8 mL; IR (neat) 3450 (ROH), 2100 (-N_3), 1725 (-C(O)O-) cm^{-1}. Further characterization was completed following separation of the diastereomers.

***trans*-6-(3-Azidopropyl)-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*trans*-18)** was isolated from the diastereomer mixture of **18** by preparative HPLC using 60% hexanes/40% ethyl acetate containing 1% 2-propanol as the solvent system: analytical HPLC (55% hexanes/45% ethyl acetate containing 1% 2-propanol, 2 cc/min) R_v 20.6 mL; ^1H NMR ($CDCl_3$) δ 4.71 (m, 1 H, 6-H), 3.88 (s, 1 H, 4-OH), 3.33–3.27 (m, 2 H, 9-H), 2.48 (2s, 2 H, 3-H), 2.00–1.57 (m, 6 H, 5-H, 7-H, and 8-H), 1.31 (s, 3 H, 4-CH_3); ^{13}C NMR ($CDCl_3$) δ 170.79 (C-2), 76.01 (C-6), 66.81 (C-4), 50.20 (C-9), 43.13 and 40.37 (C-3 and C-5), 31.64 (C-7), 28.76 (C-8), 23.65 (4-CH_3). Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.70; H, 7.09; N, 19.70. Found: C, 50.70; H, 7.02; N, 19.62.

***cis*-6-(3-Azidopropyl)-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*cis*-18)** was isolated from the diastereomer mixture of **18** by preparative HPLC using 60% hexanes/40% ethylacetate containing 1% 2-propanol as the solvent system: analytical HPLC (55% hexanes/45% ethyl acetate containing 1% 2-propanol, 2 cc/min) R_v 25.8 mL; ^1H NMR ($CDCl_3$) δ 4.23 (s, 1 H, 6-H), 3.72 (s, 1 H, 4-OH), 3.34 (m, 2 H, 9-H), 2.57 (s, 2 H, 3-H), 2.10–1.70 (m, 6 H, 5-H, 7-H, and 8-H), 1.37 (s, 3 H, 4-CH_3); ^{13}C NMR ($CDCl_3$) 171.16 (C-2), 75.89 (C-6), 67.51 (C-4), 50.09 (C-9), 43.85 and 42.05 (C-3 and C-5), 31.54 (C-7), 28.09 (C-9), 23.63 (4-CH_3). Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.70; H, 7.09; N, 19.70. Found: C, 50.89; H, 7.09; N, 19.48.

6-(3-Aminopropyl)-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one, Diastereomer Mixture (19). A solution of 1.40 g (6.57 mmol) of azide **18** in 25 mL of anhydrous methanol containing 0.24 g of platinum oxide was shaken on the Parr apparatus under 40 psi of hydrogen. The reaction was monitored by TLC using 100% ethyl acetate and was complete in 50 min. The catalyst was removed by filtration and the solvent was removed in vacuo to obtain 1.3 g (97%) of **19** as a yellow oil. The product was used in the next step without purification: IR (neat) 1735 (-C(O)O) cm^{-1}; ^{13}C NMR (D_2O) δ 176.01 and 174.82 (C-2), 72.52 and 72.50 (C-6), 68.72 and 68.62 (C-4), 47.73 and 47.58 (C-9), 40.12 and 40.08 (C-3), 39.83 and 39.65 (C-5), 27.58, 27.40, 25.76, 25.36, 23.84, and 23.64 (C-6, C-7, and 4-CH_3).

6-[[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanamido]propyl]-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one, Diastereomer Mixture (21). A mixture of 1.3 g (6.95 mmol) of amine **19** and 1.52 g (6.95 mmol) of pantothenic acid (**6**) was dissolved in 25 mL of DMF and the solution was cooled to 0 °C. To this was added 0.80 (6.95 mmol) of *N,N'*-dicyclohexylcarbodiimide. A precipitate of *N,N'*-dicyclohexylurea formed within an hour, but the reaction was allowed to proceed for 12 h at room temperature. The dicyclohexylurea was removed by filtration and the DMF was removed in vacuo. The resulting semisolid was dissolved in water and filtered. The crude product was separated by reverse-phase preparative HPLC (80% water/20% methanol). Characterization was completed following separation of the diastereomers.

***trans*-6-[3-[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanamido]propyl]-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*trans*-21)** was isolated in 7.4% yield by the reverse-phase preparative HPLC of **21**: analytical HPLC (80% water/20% methanol, 2 cc/min) R_v 18 mL; ^1H NMR (D_2O) δ 4.02 (s, 1 H, 14-H), 3.75–3.21 (m, 6 H, 9-H, 12-H, and 16-H), 2.71 (s, 2 H, 3-H), 2.63 (t, 2 H, 11-H), 2.06–1.39 (m, 6 H, 5-H, 7-H 8-H), 1.39 (s, 3 H, 4-CH_3), 0.93 (d, 6 H, 15-CH_3); ^{13}C NMR (D_2O) 175.71, 174.62, and 174.38 (C-2, C-10, and C-13), 79.19 (C-14), 76.54 (C-6), 69.13 (C-16), 68.63 (C-4), 43.45 (C-3), 40.41 (C-5), 39.79 and 39.30 (C-9 and C-12), 36.18 and 36.01 (C-6 and C-2), 32.58 and 28.94 (C-7 and C-8), 24.55 (4-CH_3), 21.16 and 19.85 (15-CH_3). Anal. Calcd for $C_{18}H_{32}N_2O_7 \cdot H_2O$: C, 53.20; H, 8.33; N, 6.90. Found: C, 53.31, H, 8.15; N, 6.60.

***cis*-6-[3-[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanamido]propyl]-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*cis*-21)** was isolated in 4.4% yield from the diastereomer mixture **21** by reverse-phase preparative HPLC: analytical HPLC (80% water/20% methanol, 2 cc/min) R_v 14 mL; ^1H NMR (D_2O) δ 4.02 (s, 1 H, 14-H), 3.72–3.16 (m, 6 H, 9-H, 12-H, and 16-H), 2.81 (d, 2 H, 3-H), 2.53 (t, 2 H, 11-H), 2.19–1.56 (m, 6 H, 5-H, 7-H, and 8-H), 1.44 (s, 3 H, 4-CH_3), 0.92 (d, 6 H, 15-CH_3); ^{13}C NMR (D_2O) δ 176.48, 175.74, 174.50 (C-2, C-10, and C-13), 78.85 (C-14), 76.55 (C-6), 69.53 (C-16), 69.13 (C-4), 44.40 (C-3), 42.49 (C-5), 39.69, 39.29 (C-9 and C-12), 36.17 and 36.01 (C-11 and C-15), 32.33 and 28.54 (C-7 and C-8), 24.69 (4-CH_3), 21.15, 19.84 (15-CH_3). Anal. Calcd for $C_{18}H_{32}N_2O_7 \cdot {}^1/_2H_2O$: C, 54.40; H, 8.31; N, 7.05. Found: C, 54.29; H, 8.20; N, 7.24.

(3,5)-*erythro*-6-[3-[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanamido]propyl]-3,5-dihydroxy-3-methylhexanoic acid, sodium salt (*erythro*-3b) was prepared in situ as described for **3a**[1] by allowing *trans*-**21** to stir in pH 10 $Na_2CO_3/NaHCO_3$ buffer solution for 6 h at room temperature. Dropwise addition of 1 N HCl to pH 7 afforded *erythro*-**3b** in neutral solution. Formation of the salt was indicated by movement of the reverse-phase HPLC peak in 80% water/20% methanol (2 mL/min) to R_v 1.8 mL. As with **3a**,[1] attempts to further acidify the solution so *erythro*-**3b** could be isolated led to immediate reappearance of the lactone peak (*trans*-**21**) at R_v 18 mL.

(3,5)-*threo*-6-[3-[[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanamido]propyl]-3,5-dihydroxy-3-methylhexanoic acid, sodium salt (*threo*-3b) was prepared from *cis*-**21** and by the procedure described for *erythro*-**3b** and was analyzed by analytical HPLC: (80% water/20% methanol, 2 mL/min) R_v 1.8 mL.

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Registry No. *erythro*-**3b** (isomer 1), 101760-13-8; *erythro*-**3b** (isomer 2), 101833-91-4; *threo*-**3b** (isomer 1), 101833-92-5; *threo*-**3b** (isomer 2), 101833-93-6; **4** (isomer 1), 101772-32-1; **4** (isomer 2),

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101759-95-9; **6**, 79-83-4; **7**, 101759-90-4; **8**, 28891-35-2; **9** (isomer 1), 101759-91-5; **9** (isomer 2), 101759-92-6; **10** (isomer 1), 101759-93-7; **10** (isomer 2), 101759-94-8; **11**, 87137-59-5; **12**, 101759-96-0; **14** (isomer 1), 101759-97-1; **14** (isomer 2), 101759-98-2; *cis*-**15**, 101760-01-4; *trans*-**15**, 101760-02-5; *cis*-**16**, 101759-99-3; *trans*-**16**, 101760-00-3; *cis*-**17**, 101760-03-6; *trans*-**17**, 101760-04-7; *cis*-**18**, 101760-05-8; *trans*-**18**, 101760-06-9; *cis*-**19**, 101760-07-0; *trans*-**19**, 101760-08-1; *cis*-**21** (isomer 1), 101760-09-2; *cis*-**21** (isomer 2), 101760-10-5; *trans*-**21** (isomer 1), 101760-11-6; *trans*-**21** (isomer 2), 101760-12-7; calcium pantothenate, 137-08-6.

Cobalt-Mediated Cyclopentenone Annulation: An Approach to the Synthesis of Cyclocolorenone

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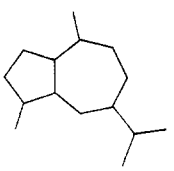
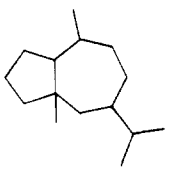
A new methodology is presented for generating the guaiane sesquiterpene skeleton as in cyclocolorenone (**4**) which features cyclopentenone annulation of a suitable cycloheptanone derivative using the sequence: propargylation by the cobalt complex $(MeC{\equiv}CCH_2)Co_2(CO)_6BF_4$ (**1a**), demetalation, regiospecific hydration to a 1,4-diketone, and base-catalyzed cyclization (Scheme I). Synthesis of the key cycloheptanone TMS enol ether **5** is foiled by the intervention of a novel cyclopropane mislocation reaction which occurs during the reaction of cycloheptadienone ketal **8** with $PhHgCBr_3$. Nonetheless, the isomeric TMS enol ether **5′** has been successfully carried through the annulation sequence of Scheme I in an efficient and highly regio- and stereoselective manner to produce the isocyclocolorenones **16′** and **16b′**. The molecular structure of the product from propargylation of **5′** by **1a** has been determined by single-crystal X-ray diffraction.

During the last several years we have been engaged in a program to explore the chemistry of (propargylium)-$Co_2(CO)_6^+$ complexes, **1**, particularly their use as electrophilic agents for carbon–carbon bond formation. Resulting from these efforts have been novel and efficient methods for the coupling of **1** with aromatics,[1] β-dicarbonyls,[2] enol derivatives,[3] allylsilanes,[4] and aluminum alkyls.[5] The propargylation of ketones (usually as their TMS ether derivatives) by **1** has been incorporated recently into a useful sequence for cyclopentenone annulation according to Scheme I.[6]

In order to further illustrate the utility of the method outlined in Scheme I, we have initiated efforts directed toward the synthesis of selected cyclopentanoid natural products. An early study using *acyclic* starting materials led to a simple, highly efficient synthesis of dihydrojasmone.[7] More challenging classes of target molecules are the guaiane (**2**) and pseudoguaiane (**3**) sesquiterpenes,



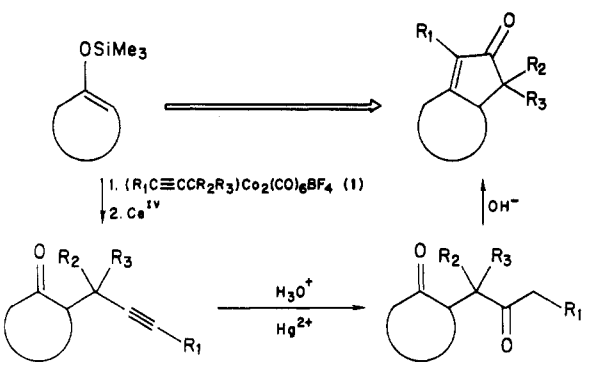
2



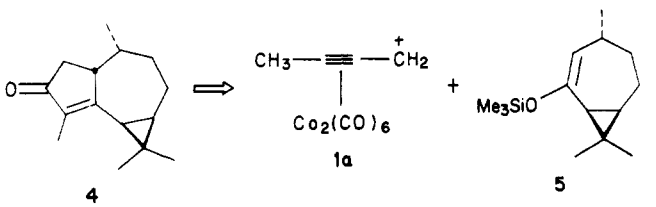
3

which, in addition to the characteristic[5,7] hydroazulenic skeleton, also feature several stereocenters. These compounds have been the object of intense synthetic efforts during the last ten years,[8] in part because of the significant cytotoxic and antitumor activity of several members.[9] Perusal of the syntheses reported to date reveals: (1) that most generate the azulenic skeleton by rearrangement of decalone derivatives[10] or start from natural products already possessing the bicyclo[5.3.0] framework;[11] (2) that stereochemical control remains a major challenge; and (3) that few guaianes (**2**) have been successfully synthesized.

Scheme I



Scheme II



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