A Simple Acid-Catalyzed Isomerization of γ-Hydroxy Enones into γ-Diones

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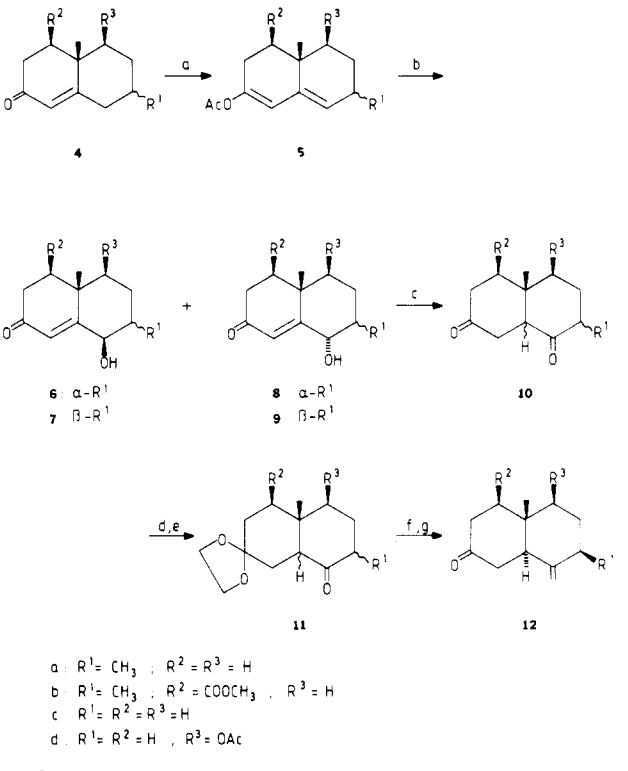
The acid-catalyzed isomerization of γ-hydroxy α,β-unsaturated ketones into γ-diones can be performed in high yields by using hydrogen bromide in ether. The utility of this functional group transformation is illustrated by its application to the synthesis of key intermediates **12a** and **12b** for rearranged drimanes, in steroid functionalization, and in the total synthesis of (±)-7-hydroxycostal.

In a recent paper we described a method for the synthesis of methylene ketones with general structure **3** (R^1 = H) which are used as key intermediates in the total synthesis of eudesmanes.[1] In this method an oxidation–reduction procedure was used for the conversion of γ-hydroxy α,β-enones **1** into γ-diones **2**. Later we discovered a simple one-step isomerization for the transformation of **1** into **2** with hydrogen bromide in ether.

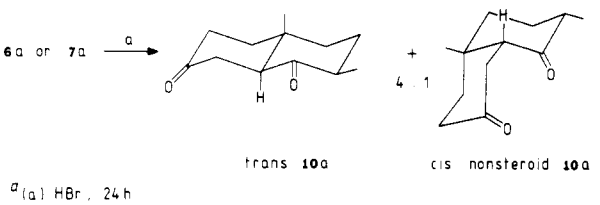
In the present paper we have extended our studies of the latter reaction to emphasize the utility of this simple transformation in several areas of natural product synthesis. The method was investigated first for the synthesis of methylene ketones **12a** and **12b** which are suitable intermediates in the synthesis of sesquiterpenes possessing a rearranged drimane skeleton like muzigadial, a strong insect antifeedant.[2] The starting compounds **4a** and **4b** were prepared according to standard Robinson annelation procedures; the enones were obtained as 2:1 mixtures of their axial- and equatorial-methyl epimers, respectively[3] (Scheme I). An improved conversion of the enones **4** into the dienol acetates **5** with acetic anhydride, chlorotrimethylsilane, and sodium iodide[4] proceeded smoothly and in almost quantitative yield.

The *m*-chloroperbenzoic acid oxidation of dienol acetate **5a** as a mixture of two epimers, afforded a 10:5:1.5:1 mixture of **6a**, **7a**, **8a**, and **9a**, respectively, in 77% yield. After column chromatography and recrystallization the major products **6a** and **7a** could be isolated in pure form in 13% and 7.5%, respectively. The stereochemistry of the hydroxyl group in **6a** and **7a** was assigned on the basis of a pronounced change in the ^{1}H NMR chemical shift of both angular methyl signals in **6a** and **7a**, when Eu(fod)$_3$ was added.[5] Since the dienol acetate **5a** was a 2:1 mixture of C-7 axial- and C-7 equatorial-methyl isomers[6] the position of the C-7 methyl group in **6a** and **7a** was obvious. This latter datum, together with ^{1}H NMR studies and the general reaction outcome of the *m*-chloroperbenzoic acid oxidation,[1,7] confirmed our stereochemical assignments concerning **8a** and **9a**. The *m*-chloroperbenzoic acid oxidation of **5b** afforded the hydroxy enones **6b**, **7b**, **8b**, and **9b** in comparable yields.

Scheme I[a]



Scheme II[a]



The key step of the procedure was the acid-catalyzed isomerization of the γ-hydroxy enones **6–9** into the diones **10**. Treatment of a mixture of **6a–9a** with hydrogen bromide *for 1 h* afforded dione **10a** as a mixture of stereoisomers in nearly quantitative yield. After column chromatography the cis nonsteroid isomer of **10a**[8] could be isolated in pure form. Hydrogen bromide treatment of pure **6a** or pure **7a** *for 1 day* both afforded a 4:1 mixture of the trans and cis nonsteroid isomer of **10a**, respectively (Scheme II). In both isomers the stereochemistry of the

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(2) Kubo, I.; Miura, I.; Pettei, M. J.; Lee, Y.-W.; Pilkiewicz, F.; Nakanishi, K. *Tetrahedron Lett.* **1977**, 4553.
(3) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In "The total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1983; Vol. V, p 129.
(4) Chowdhury, P. K.; Sharma, R. P.; Barua, J. N. *Tetrahedron Lett.* **1983**, *24*, 3383.
(5) An addition of 4.8 mg of Eu(fod)$_3$ to a solution of 6.0 mg of **6a** in 0.5 mL of carbon tetrachloride caused a change of δ 0.71 in the ^{1}H NMR chemical shift of the angular methyl signal. In a similar way for **7a** a change of δ 0.64 was found.
(6) The numbering system follows the designations used in the Experimental Section.
(7) Holland, H. L.; Auret, B. J. *Can. J. Chem.* **1975**, *53*, 2041.
(8) (a) Williamsen, K. L.; Sloan, L. R.; Howell, T.; Spencer, T. A. *J. Org. Chem.* **1966**, *31*, 436. (b) House, H. O.; Lusch, M. J. *Ibid.* **1977**, *42*, 183.

0022-3263/85/1950-2650$01.50/0

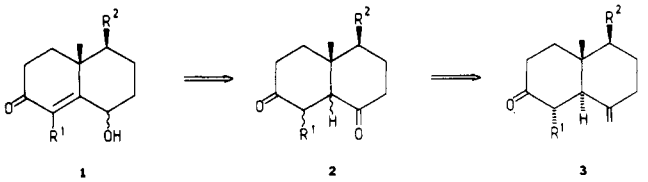
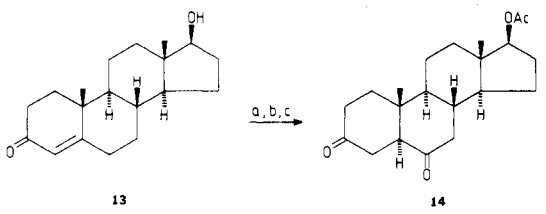


Figure 1.

Scheme III[a]



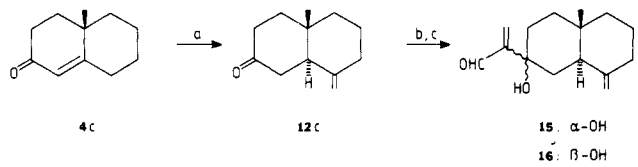
[a] (a) Ac_2O, $(CH_3)_3SiCl$, NaI; (b) MCPBA; (c) HBr.

C-2 methyl group was assigned to be equatorial, because of the presence of a large diaxial coupling constant (J = 12.5 Hz) in the ^1H NMR signal of the C-2 proton.

A similar product ratio was found when pure trans **10a** or pure cis nonsteroid **10a** was treated with hydrogen bromide for 1 day. These data clearly show that after prolonged hydrogen bromide treatment isomerization and subsequent epimerization occur. Similar results were found when a mixture of **6b–9b** was treated with hydrogen bromide. A prolonged reaction time also caused epimerization leading to a 2:1 mixture of the trans and cis nonsteroid isomer of **10b**, respectively, but under these conditions some hydrolysis of the ester function can occur. Therefore a short reaction time (1 h) was prefered. Although mixtures of stereoisomers were obtained in this stage of the procedure, this fact was not a serious drawback since treatment of the isomer mixtures of **10a** and **10b**, respectively, with 2-butanone dioxolane[9] in the presence of *p*-toluenesulfonic acid monohydrate followed by epimerization with methanolic potassium hydroxide simplified the product composition considerably.

Following this procedure **11a** could be isolated as a 4:1 mixture of the trans- and cis-fused isomer, respectively, in 67% yield. In a similar way **10b** afforded exclusively **11b** as the trans-fused product in 88% yield. A further simplification occurred upon treatment of the 4:1 mixture of **11a** with methylenetriphenylphosphorane in dimethyl sulfoxide[11] and subsequent hydrolysis of the acetal function. This procedure gave the methylene ketone **12a** in 67% yield.[12] In a similar way **11b** gave the methylene keto ester **12b** in 50% yield.[12,13] The potential use of the method in functional group transformations in steroids was illustrated by the conversion of testosterone (**13**) into (5α,17β)-17-(acetyloxy)androstane-3,6-dione (**14**)[15] (Scheme III). In an overall yield of 80% the trans-fused product **14** was isolated exclusively.

Scheme IV[a]



[a] (a) see Scheme I; (b) $CH_2{=}C(Li)CH(OEt)_2$; (c) H_3^+O, acetone.

Finally the conversion of **4c** into the fungitoxic (±)-7-hydroxycostal (**15**)[16] and its epimer **16** in 36% overall yield again stress the applicability of the method in the total synthesis of eudesmanes (Scheme IV).

The conversion of **4c** into **12c** proceeded as outlined in Scheme I.[17] The addition of (1,1-diethoxy-2-propen-2-yl)lithium[18] and subsequent hydrolysis of the diethyl acetal function gave a 2:1 mixture of (±)-7-hydroxycostal (**15**) and its C-7 epimer **16**, respectively, in 79% yield. The epimers could be separated by preparative chromatography and in a thin-layer chromatographic bioassay,[19] both compounds proved to inhibit spore germination of the test fungus *Cladosporium cucumerinum* in the same degree.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were determined on a Bruker CXP-300 or a Varian EM-390 spectrometer. Chemical shifts are reported in δ units from the internal standard tetramethylsilane in chloroform-*d* as the solvent, unless otherwise noted. Mass spectral data and exact mass measurements were obtained with AEI MS 902 and VG Micromass 7070F spectrometers. GC Analyses were carried out on a Varian Vista 6000 chromatograph. The column used for determining product ratio was a 2-m column packed with 3% SP-2250 on Chromosorb-W. Solvents were dried with anhydrous sodium sulfate prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

***cis,trans*-(±)-4,4a,5,6,7,8-Hexahydro-4a,7-dimethyl-2-(3*H*)-naphthalenone (4a).**[20] The enone **4a** was prepared from 2,5-dimethylcyclohexanone[21] (21.05 g, 0.167 mol) and 20 mL of 3-buten-2-one by the method of Heathcock et al.:[22] yield 13.56 g (45%). According to GCMS and ^1H NMR enone **4a** was a 2:1 mixture of two stereoisomers,[3] **4a** (trans isomer) [^1H NMR (major peaks) δ 0.91 (d, J = 7 Hz, 3 H), 1.26 (s, 3 H); mass spectrum, m/e (relative intensity) 178 (M^+, 80), 150 (60), 136 (100), 135 (45), 121 (69)] and **4a** (cis isomer) [^1H NMR (major peaks) δ 1.00 (d, J = 6 Hz, 3 H), 1.23 (s, 3 H); mass spectrum, m/e (relative intensity) 178 (M^+, 92), 150 (55), 136 (100), 135 (47), 121 (69)], respectively.

(1α,6α,β,8aα)-(±)-1,2,3,5,6,7,8,8a-Octahydro-6,8a-dimethyl-3-oxo-1-naphthalenecarboxylic Acid Methyl Ester (4b). The enone **4b** was prepared from 2,5-dimethylcyclohexanone[21] (12.60 g, 0.100 mol) and 1.2 equiv of methyl 4-oxo-2-pentenoate by the procedure of McMurry et al.:[23] yield 6.37 g (27%). According to GCMS and ^1H NMR enone **4b** was a 2:1 mixture of two stereoisomers,[3,24] **4b** (1α,6β,8aα-isomer) [^1H NMR

(9) In contrast to **10c** and **10d**[10] the diones **10a** and **10b** showed no different behavior upon treatment with trimethyl orthoformate or 2-butanone dioxolane.[1]

(10) Starting from the enone **4d** the procedure described here gave **10d** in an overall yield of 72%.

(11) Greenwald, R.; Chaykovski, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

(12) During this reaction, according to GCMS, small amounts (<10%) of stereoisomers of **12a** and **12b** were formed. Stereoisomer of **12a**: mass spectrum, m/e (relative intensity) 192 (M^+, 66), 177 (40), 135 (57), 121 (43), 68 (100). Stereoisomer of **12b**: mass spectrum, m/e (relative intensity) 250 (M^+, 42), 235 (40), 191 (41), 135 (66), 121 (100), 107 (52).

(13) The yield of **12b** was lowered by reaction of its ester function with the Wittig reagent.[14]

(14) Uijttewaal, A. P.; Jonkers, F. L.; van der Gen, A. *J. Org. Chem.* **1979**, *44*, 3157.

(15) Baumgarth, M.; Irmscher, K. *Tetrahedron* **1975**, *31*, 3119.

(16) Schneider, J. A.; Nakaniski, K. *J. Chem. Soc., Chem. Commun.* **1983**, 353.

(17) Starting from enone **4c** compound **12c** was obtained in an overall yield of 45% as described.[1]

(18) Depezay, J.-C.; Le Merrer, Y. *Bull. Soc. Chim. Fr.* **1981**, 306.

(19) Homans, A. L.; Fuchs, A. *J. Chromatogr.* **1970**, *51*, 327.

(20) Könst, W. M. B.; Witteveen, J. G.; Boelens, H. *Tetrahedron* **1976**, *32*, 1415.

(21) Kornfeld, E. C.; Jones, R. G.; Parke, T. V. *J. Am. Chem. Soc.* **1949**, *71*, 150.

(22) Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.

(23) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217.

(major peaks) δ 0.91 (d, J = 7 Hz, 3 H), 1.24 (s, 3 H), 3.71 (s, 3 H); mass spectrum, m/e (relative intensity) 236 (M^+, 78), 221 (56), 205 (27), 177 (79), 150 (100), 135 (75), 121 (84)] and **4b** (1α,6α,8aα-isomer) [^{1}H NMR (major peaks) δ 0.99 (d, J = 6 Hz, 3 H), 1.21 (s, 3 H) 3.68 (s, 3 H); mass spectrum, m/e (relative intensity) 236 (M^+, 94), 221 (25), 205 (27), 177 (76), 150 (100), 135 (66), 121 (83)], respectively.

Dienol Acetates 5. General Procedure. A solution of 4 and 4 equiv of sodium iodide in acetic anhydride was treated with chlorotrimethylsilane at 0 °C under a nitrogen atmosphere for 1–2 h according to the procedure as described by Sharma et al.[4] The reaction mixture was concentrated in vacuo, dissolved in ethyl acetate, washed with 2% sodium thiosulfate and saturated sodium bicarbonate, and dried. Filtration and evaporation under reduced pressure afforded the dienol acetates **5** (90–100%). According to ^{1}H NMR the so-obtained dienol acetates **5** were pure and used immediately for the next reaction.

***cis,trans*-(±)-3,4,4a,5,6,7-Hexahydro-4a,7-dimethyl-2-naphthalenol acetate (5a)**: yield 92%; a colorless oil which, according to ^{1}H NMR and GLC, was a 2:1 mixture of the trans and cis isomer of **5a**, respectively. ^{1}H NMR δ 0.95 (d, J = 7 Hz, *trans*-CH_3), 0.98 (d, J = 6 Hz, *cis*-CH_3), 1.03 (s, 3 H), 1.17–2.83 (m, 9 H), 2.13 (s, 3 H), 5.27 (m, 1 H), 5.67 (d, J = 1.5 Hz, 1 H).

(1α,6α,β,8aα)-(±)-3-(Acetyloxy)-1,2,6,7,8,8a-hexahydro-6,8a-dimethyl-1-naphthalenecarboxylic acid methyl ester (5b): yield 99%; a colorless oil which, according to ^{1}H NMR and GLC, was a 2:1 mixture of the 6β- and 6α-isomer of **5b**, respectively. ^{1}H NMR δ 0.98 (d, J = 7 Hz, β-CH_3), 1.00 (d, J = 6 Hz, α-CH_3), 1.10 (br s, 3 H), 1.19–3.06 (m, 8 H), 2.13 (s, 3 H), 3.68 (s, 3 H), 5.35 (m, 1 H), 5.70 (d, J = 1.5 Hz, 1 H).

***m*-Chloroperbenzoic Acid Oxidation.** A sample of dienol acetate **5a** (7.98 g, 36.27 mmol) was treated with *m*-chloroperbenzoic acid according to the procedure as described earlier.[1] The workup and column chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (5:1 to 1:1) gave, according to ^{1}H NMR, 5.43 g (77%) of a 10:5:1.5:1 mixture of **6a**, **7a**, **8a**, and **9a**, respectively. Recrystallization of the proper fractions yielded 0.93 g of pure **6a** and 0.54 g of pure **7a**. The hydroxy enones **8a** and **9a** could not be isolated in pure form. In a similar way a sample of dienol acetate **5b** (3.85 g, 13.85 mmol) gave 2.56 g (73%) of a mixture of **6b**, **7b**, **8b**, and **9b**.

(4aα,7β,8α)-(±)-4,4a,5,6,7,8-Hexahydro-4a,7-dimethyl-8-hydroxy-2(3*H*)-naphthalenone (6a): mp 87–89 °C (from petroleum ether (bp 40–60 °C)); ^{1}H NMR δ 0.89 (d, J = 7 Hz, 3 H), 1.10–2.83 (m, 10 H), 1.46 (s, 3 H), 3.97 (t, J = 1.5 Hz, 1 H), 5.79 (s, 1 H); mass spectrum, m/e (relative intensity) 194 (M^+, 100), 179 (83), 137 (43), 124 (38), 123 (58), 110 (29), 109 (50). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.46; H, 9.47.

(4aα,7α,8α)-(±)-4,4a,5,6,7,8-Hexahydro-4a,7-dimethyl-8-hydroxy-2(3*H*)-naphthalenone (7a): mp 78–80 °C (from petroleum ether (bp 40–60 °C)); ^{1}H NMR δ 1.04 (d, J = 6 Hz, 3 H), 1.20–2.85 (m, 10 H), 1.40 (s, 3 H), 4.04 (t, J = 1.5 Hz, 1 H), 5.74 (s, 1 H); mass spectrum, m/e (relative intensity) 194 (M^+, 100), 179 (84), 137 (36), 124 (40), 123 (53), 110 (29), 109 (51). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.38; H, 9.41.

(4aα,7β,8β)-(±)-4,4a,5,6,7,8-Hexahydro-4a,7-dimethyl-8-hydroxy-2(3*H*)-naphthalenone (8a): ^{1}H NMR (main peaks) δ 0.83 (d, J = 7 Hz, 3 H), 1.25 (s, 3 H), 4.47 (dd, J = 1.5, 5 Hz, 1 H), 6.13 (d, J = 1.5 Hz, 1 H); mass spectrum, m/e (relative intensity) 194 (M^+, 61), 179 (26), 138 (45), 124 (24), 123 (48), 110 (100), 109 (96).

(4aα,7α,8β)-(±)-4,4a,5,6,7,8-Hexahydro-4a,7-dimethyl-8-hydroxy-2(3*H*)-naphthalenone (9a): ^{1}H NMR (main peaks) δ 0.84 (d, J = 6 Hz, 3 H), 1.22 (s, 3 H), 3.86 (br d, J = 7.5 Hz, 1 H), 6.16 (d, J = 1.5 Hz, 1 H); mass spectrum, m/e (relative intensity) 194 (M^+, 100), 179 (27), 138 (41), 137 (30), 124 (45), 123 (57), 110 (80), 109 (95).

(1α,5α,6β,8aα)-(±)-1,2,3,5,6,7,8,8a-Octahydro-6,8a-dimethyl-5-hydroxy-3-oxo-1-naphthalenecarboxylic acid methyl ester (6b): mp 133–134 °C (from diisopropyl ether); ^{1}H NMR δ 0.90 (d, J = 7 Hz, 3 H), 1.17–3.20 (m, 9 H), 1.43 (s, 3 H), 3.71 (s, 3 H), 4.03 (t, J = 1.5 Hz, 1 H), 5.85 (s, 1 H); mass spectrum, m/e (relative intensity) 252 (M^+, 100), 234 (33), 220 (94), 165 (25), 138 (26). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.34; H, 7.92.

(1α,5α,6α,8aα)-(±)-1,2,3,5,6,7,8,8a-Octahydro-6,8a-dimethyl-5-hydroxy-3-oxo-1-naphthalenecarboxylic acid methyl ester (7b): mp 121–122 °C (from diisopropyl ether); ^{1}H NMR δ 1.06 (d, J = 6 Hz, 3 H), 1.23–3.17 (m, 9 H), 1.40 (s, 3 H), 3.71 (s, 3 H), 4.13 (br s, 1 H), 5.81 (s, 1 H); mass spectrum, m/e (relative intensity) 252 (M^+, 100), 234 (22), 220 (76), 165 (14), 148 (26), 138 (22), 137 (26), 87 (33). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.46; H, 7.85.

(1α,5β,6β,8aα)-(±)-1,2,3,5,6,7,8,8a-Octahydro-6,8a-dimethyl-5-hydroxy-3-oxo-1-naphthalenecarboxylic acid methyl ester (8b): ^{1}H NMR (main peaks) δ 0.86 (d, J = 7 Hz, 3 H), 1.24 (s, 3 H), 3.71 (s, 3 H), 4.54 (dd, J = 1.5, 5 Hz, 1 H), 6.23 (d, J = 1.5 Hz, 1 H).

(1α,5β,6α,8aα)-(±)-1,2,3,5,6,7,8,8a-Octahydro-6,8a-dimethyl-5-hydroxy-3-oxo-1-naphthalenecarboxylic acid methyl ester (9b): ^{1}H NMR (main peaks) δ 0.86 (d, J = 6 Hz, 3 H), 1.21 (s, 3 H), 3.71 (s, 3 H), 3.91 (br d, J = 7.5 Hz, 1 H), 6.28 (d, J = 1.5 Hz, 1 H).

Acid-Catalyzed Isomerization. (±)-Octahydro-2,4a-dimethyl-1,7-naphthalenedione (10a). To a solution of 3.67 g of a mixture of **6a**, **7a**, **8a**, and **9a** (18.91 mmol) in 100 mL of ether was added 0.5 mL of concentrated hydrogen bromide. The reaction mixture was stirred at room temperature for 1 h, neutralized with triethylamine, washed with brine, and dried. Filtration and evaporation under reduced pressure afforded 3.62 g of a brown-red oil. Column chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (3:1) gave 3.45 g (93%) of **10a** which, according to GCMS, was a mixture of stereoisomers: mass spectra (major fragments), m/e 194 (M^+), 165, 137, 124, 111, 110, 109. Recrystallization of one of the fractions yielded the pure 2α,4aβ,8aβ-isomer of **10a** as a white solid: mp 99–101 °C (from diisopropyl ether); ^{1}H NMR δ 1.00 (d, J = 6.5 Hz, 3 H), 1.33 (m, 1 H), 1.35 (s, 3 H), 1.46–1.80 (m, 3 H), 1.87–2.05 (m, 2 H), 2.24–2.40 (m, 3 H), 2.44 (m, J = 6, 6.5, 12.5 Hz, 1 H), 2.63–2.77 (m, 2 H); mass spectrum, m/e (relative intensity) 194 (M^+, 72), 179 (13), 137 (12), 124 (26), 111 (100), 110 (41), 109 (21). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.50. A sample of **6a** (0.029 g, 0.15 mmol) was treated for 24 h as described above. The workup and purification by preparative-layer chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (4:1) afforded 0.018 g (62%) of the 2α,4aα,8aβ-isomer of **10a** as a light yellow oil: ^{1}H NMR (C_6D_6) δ 0.57 (s, 3 H), 1.09 (d, J = 6 Hz, 3 H), 1.13–1.39 (m, 5 H), 1.61 (m, 1 H), 1.84 (m, J = 6, 6.5, 12.5 Hz, 1 H), 1.89–2.07 (m, 2 H), 2.19 (m, 1 H), 2.48–2.54 (m, 2 H); mass spectrum, m/e (relative intensity), 194 (M^+, 57), 179 (12), 165 (100), 137 (80), 124 (23), 111 (30), 110 (16), 109 (24); calcd for $C_{12}H_{18}O_2$ (M^+) m/e 194.1305, found m/e 194.1308 and 0.005 g (17%) of the 2α,4aβ,8aβ-isomer of **10a**. A similar result was found when **7a** was treated with hydrogen bromide for 24 h.

(±)-Decahydro-6,8a-dimethyl-3,5-dioxo-1-naphthalenecarboxylic Acid Methyl Ester (10b). A sample of a mixture of **6b**, **7b**, **8b**, and **9b** (1.47 g, 5.83 mmol) was treated with concentrated hydrogen bromide as described above. The workup gave 1.47 g of a yellow oil which, according to GCMS, was a mixture of stereoisomers of **10b**. A sample of 0.44 g of this mixture was chromatographed on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (3:1 to 2:1), and give in order of elution 0.15 g (34%) of, according to GCMS, a mixture of two stereoisomers of **10b**, mass spectrum (major fragments), m/e 252 (M^+), 193, 165, 137, 124, 111, 81, and 0.21 g (48%) of, according to GCMS, a nearly pure isomer of **10b**, mass spectrum (major fragments) m/e 252 (M^+) 193, 165, 142, 124, 111 (base peak), 82, 81.

A sample of a mixture of **6b** and **7b** (0.044 g, 0.17 mmol) was treated for 24 h as described above. The workup and purification by preparative-layer chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (4:1) afforded 0.026 g (59%) of the 1α,4aβ,6α,8aα-isomer of **10b** as a white solid [mp 105–106 °C (from diisopropyl ether); ^{1}H NMR δ 1.02 (s, 3 H), 1.06 (d, J = 6 Hz, 3 H), 1.37–2.90 (m, 11 H), 3.74 (s, 3 H); mass spectrum, m/e (relative intensity) 252 (M^+, 15), 193 (14), 165 (100), 137 (24), 124 (22), 111 (18), 81 (21); calcd for $C_{14}H_{20}O_4$ (M^+) m/e 252.1359, found m/e 252.1352] and 0.014 g (32%) of the 1α,4aα,6β,8aα-

(24) The cis stereochemistry of the ester and angular methyl group in **4b** was assigned based on the literature.[25]

(25) McMurry, J. E.; Blaszczak, L. C.; Johnson, M. A. *Tetrahedron Lett.* **1978**, 1633.

isomer of **10b** as a white solid: mp 97–98 °C (from diisopropyl ether); ^{1}H NMR δ 1.05 (d, J = 6 Hz, 3 H), 1.37 (s, 3 H), 1.50–2.97 (m, 11 H), 3.73 (s, 3 H); mass spectrum, m/e (relative intensity) 252 (M^+, 23), 193 (15), 165 (32), 142 (27), 124 (22), 111 (100), 82 (43), 81 (27); calcd for $C_{14}H_{20}O_4$ (M^+) m/e 252.1359, found m/e 252.1345.

(4′aα,7′α,8′aα,β)-(±)-Octahydro-4′a,7′-dimethylspiro[1,3-dioxolane-2,2′(8′H)-naphthalen]-8′-one (11a). To a solution of a stereoisomer mixture of **10a** (1.25 g, 6.44 mmol) in 15 mL of 2-butanone dioxolane were added catalytic amounts of ethylene glycol and p-toluenesulfonic acid monohydrate. The reaction mixture was stirred at room temperature for 20 h, and then 0.25 mL of triethylamine was added. The reaction mixture was taken up in 50 mL of ether, washed with brine, and dried. After filtration and evaporation under reduced pressure the residual oil was dissolved in 50 mL of a 1% solution of potassium hydroxide in methanol and stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, dissolved in 150 mL of dichloromethane, washed with water and brine, and dried. Filtration and evaporation under reduced pressure afforded an oil which was chromatographed on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (5:1). According to GCMS and ^{1}H NMR the resulting colorless oil (1.02 g, 67%) was a 4:1 mixture of two stereoisomers, **11a** (trans-fused isomer) [^{1}H NMR (major peaks) δ 0.79 (s, 3 H), 1.02 (d, J = 6 Hz, 3 H), 3.94 (s, 4 H); mass spectrum, m/e (relative intensity) 238 (M^+, 12), 99 (100)] and **11a** (cis-fused isomer) [^{1}H NMR (major peaks) δ 0.90 (s, 3 H), 1.02 (d, J = 6 Hz, 3 H), 3.94 (s, 4 H); mass spectrum, m/e (relative intensity) 238 (M^+, 12), 99 (100)], respectively.

(4′α,4′aα,7′α,8′aβ)-(±)-Octahydro-4′a,7′-dimethyl-8′-oxospiro[1,3-dioxolane-2,2′(1′H)-naphthalene]-4′-carboxylic Acid Methyl Ester (11b). A sample of a stereoisomer mixture of **10b** (0.90 g, 3.56 mmol) was treated as described above. The workup and column chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (3:1) afforded 0.931 g (88%) of a white solid, which according to ^{1}H NMR, was pure **11b**: mp 110–112 °C (from diisopropyl ether); ^{1}H NMR δ 0.81 (s, 3 H), 0.99 (d, J = 6 Hz, 3 H), 1.20–2.86 (m, 11 H), 3.67 (s, 3 H), 3.92 (br s, 4 H); mass spectrum, m/e (relative intensity) 296 (M^+, 5), 268 (12), 237 (11), 209 (93), 157 (82), 139 (25), 99 (35), 86 (100). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.93; H, 8.01.

(4aα,7α,8aβ)-(±)-Octahydro-4a,7-dimethyl-8-methylene-2-(1H)-naphthalenone (12a). The procedure of Corey et al.[11] was employed by using 10 mL of 0.87 M (dimethylsulfinyl)sodium in dimethyl sulfoxide, 3.09 g of methyltriphenylphosphonium bromide (8.66 mmol), and 1.03 g of a 4:1 mixture of the trans and cis isomer of **11a** (4.33 mmol) in 15 mL of dimethyl sulfoxide. The reaction mixture was stirred at 50 °C under a nitrogen atmosphere for 3.5 h. After the workup the residue was dissolved in a mixture of 50 mL of acetone and 5 mL of 1 N hydrogen chloride and stirred at room temperature for 20 h. The mixture was concentrated at room temperature under reduced pressure and the residue was taken up in 75 mL of dichloromethane, washed with 50 mL of saturated sodium bicarbonate and brine, and dried. After filtration and evaporation under reduced pressure the residue was chromatographed on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (20:1) and afforded 0.556 g (67%) of **12a** as a white solid.[26] Recrystallization from petroleum ether (bp 40–60 °C) at −30 °C gave 0.485 g of pure **12a**: mp 66–67 °C; ^{1}H NMR δ 0.94 (s, 3 H), 1.10 (d, J = 6 Hz, 3 H), 1.17–2.73 (m, 12 H), 4.47 (br s, 1 H), 4.79 (br s, 1 H); mass spectrum, m/e (relative intensity) 192 (M^+, 84), 177 (42), 135 (100), 68 (65). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.14; H, 10.54.

(1α,4aβ,6α,8aα)-(±)-Decahydro-6,8a-dimethyl-5-methylene-3-oxo-1-naphthalenecarboxylic Acid Methyl Ester (12b). The procedure described above was employed by using 10 mL of 0.48 M (dimethylsulfinyl)sodium in dimethyl sulfoxide, 1.73 g of methyltriphenylphosphonium bromide (4.85 mmol), and 0.46 g of **11b** (1.55 mmol) in 10 mL of dimethyl sulfoxide. The resulting product was hydrolyzed with 50 mL of methanol and 10 mL of 6.5 N hydrogen chloride at room temperature for 20 h as described above. The workup and column chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (15:1 to 10:1) afforded 0.192 g (50%) of **12b** as a white solid.[26] Recrystallization from diisopropyl ether gave 0.163 g of pure **12b**: mp 128–130 °C; ^{1}H NMR δ 0.96 (s, 3 H), 1.07 (d, J = 6 Hz, 3 H), 1.20–3.00 (m, 11 H), 3.71 (s, 3 H), 4.54 (br s, 1 H), 4.85 (br s, 1 H); mass spectrum, m/e (relative intensity) 250 (M^+, 35), 235 (37), 191 (56), 135 (100), 121 (96), 107 (66). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.13; H, 8.63.

(5α,17β)-17-(Acetyloxy)androstane-3,6-dione (14).[15] A sample of testosterone (**13**) (0.87 g, 3.00 mmol) was treated with acetic anhydride, chlorotrimethylsilane, and sodium iodide as described above. The workup gave 1.12 g (100%) of a white solid, which according to ^{1}H NMR was pure (17β)-androsta-3,5-diene-3,17-diol diacetate:[27] ^{1}H NMR (main peaks) δ 0.85 (s, 3 H), 1.03 (s, 3 H), 2.06 (s, 3 H), 2.14 (s, 3 H), 4.60 (dd, J = 6, 10 Hz, 1 H), 5.37 (t, J = 3 Hz, 1 H), 5.68 (br s, 1 H). This solid (1.12 g, 3.00 mmol) was treated with m-chloroperbenzoic acid as described.[1] The workup and purification by column chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (3:1 to 1:1) afforded 0.84 g (80%) of a 3.6:1 mixture of (6β,17β)-[15] and (6α,17β)-17-(acetyloxy)-6-hydroxyandrost-4-en-3-one,[28] respectively. A sample of this mixture (0.57 g, 1.65 mmol) was treated with concentrated hydrogen bromide as described above. The workup gave 0.57 g (100%) of (5α,17β)-17-(acetyloxy)-androstane-3,6-dione (**14**).

(2α,4aβ,8aα)-(±)-Decahydro-2-hydroxy-4a-methyl-α,8-bis(methylene)-2-naphthaleneacetaldehyde ((±)-7-Hydroxycostal) (15) and Its (2α,4aα,8aβ)-(±)-Epimer (16). To a solution of 2.57 g of 2-bromo-3,3-diethoxy-1-propene[18] (12.30 mmol) in 10 mL of dry tetrahydrofuran was added dropwise at −80 °C 7.7 mL of a 15% solution of butyllithium in hexane. The mixture was stirred at −80 °C for 15 min and then a solution of 1.45 g of **12c**[17] (8.15 mmol) in 10 mL of dry tetrahydrofuran was added dropwise over a period of 10 min. The mixture was allowed to warm to room temperature and stirring was continued at room temperature for 20 h. At −80 °C the mixture was neutralized with saturated ammonium chloride, poured into water (100 mL), and extracted with ether (4 × 50 mL). The combined organic layers were concentrated at room temperature under reduced pressure, and the residue was taken up in 30 mL of acetone, containing 1 mL of 1 N hydrogen chloride. The mixture was stirred at room temperature for 3 h, poured into water (50 mL), and extracted with dichloromethane (4 × 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (50 mL) and brine and dried. Filtration and evaporation at room temperature under reduced pressure afforded an oil which was chromatographed on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (5:1). According to ^{1}H NMR the resulting colorless oil (1.51 g) was a 2:1 mixture of **15** and **16** (yield 79%). After column chromatography on silica gel with petroleum ether (bp 40–60 °C)/ethyl acetate (15:1 to 5:1) both compounds were obtained in pure form. Compound **15** ((±)-7-hydroxycostal) had identical spectral characteristics with those reported in the literature.[16] Its epimer **16**: mp 87–88 °C (from petroleum ether (bp 40–60 °C)); ^{1}H NMR δ 0.80 (s, 3 H), 1.00–2.50 (m, 13 H), 3.77 (br s, 1 H, exchanges with D_2O), 4.47 (br s, 1 H), 4.73 (br s, 1 H), 6.17 (s, 1 H), 6.50 (s, 1 H), 9.51 (s, 1 H); mass spectrum, m/e (relative intensity) 234 (M^+, 1.5 %), 216 (31), 201 (23), 123 (100); calcd for $C_{15}H_{22}O_2$ (M^+) m/e 234.1620, found m/e 234.1629.

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Registry No. (±)-*cis*-**4a**, 96616-86-3; (±)-*trans*-**4a**, 96616-87-4; (±)-(1α,6β,8aα)-**4b**, 96616-88-5; (±)-(1α,6α,8aα)-**4b**, 96616-89-6; (±)-*cis*-**5a**, 96616-90-9; (±)-*trans*-**5a**, 96616-91-0; (±)-6β-**5b**, 96616-92-1; (±)-6α-**5b**, 96616-93-2; (±)-**6a**, 96616-94-3; (±)-**6b**, 96616-98-7; (±)-**7a**, 96616-95-4; (±)-**7b**, 96616-99-8; (±)-**8a**, 96616-96-5; (±)-**8b**, 96617-00-4; (±)-**9a**, 96616-97-6; (±)-**9b**, 96617-01-5; (±)-(2α,4aβ,8aβ)-**10a**, 96617-02-6; (±)-(2α,4aα,8aβ)-**10a**, 96617-03-7; (±)-(1α,4aβ,6α,8aα)-**10b**, 96617-04-8; (±)-

(26) A small amount of a stereoisomer was present.[12]

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(1α,4aα,6β,8aα)-**10b**, 96617-05-9; (±)-**11a** (trans-fused), 96617-06-0; (±)-**11a** (cis-fused), 96647-96-0; (±)-**11b**, 96617-07-1; (±)-**12a**, 96617-08-2; (±)-**12b**, 96617-09-3; (±)-**12c**, 87332-41-0; **13**, 58-22-0; **14**, 25469-53-8; (±)-**15**, 96479-43-5; (±)-**16**, 96647-97-1; (17β)-androsta-3,5-diene-3,7-diol diacetate, 1778-93-4; (6β,17β)-17-(acetyloxy)-6-hydroxyandrost-4-en-3-one, 13096-48-5; (6α,17β)-17-(acetyloxy)-6-hydroxyandrost-4-en-3-one, 13573-36-9; 2-bromo-3,3-diethoxy-1-propene, 17592-40-4; 3-buten-2-one, 78-94-4; 2,5-dimethylcyclohexanone, 932-51-4; methyl 4-oxo-2-pentenoate, 4188-88-9; methyltriphenylphosphonium bromide, 1779-49-3.

Synthesis of the *cyclo*-[(gly)Thz-(*R*)- and *cyclo*-[(gly)Thz-(*S*)-(gln)Thz-L-Val-L-Leu-L-Pro] Isomers of Dolastatin 3[1a]

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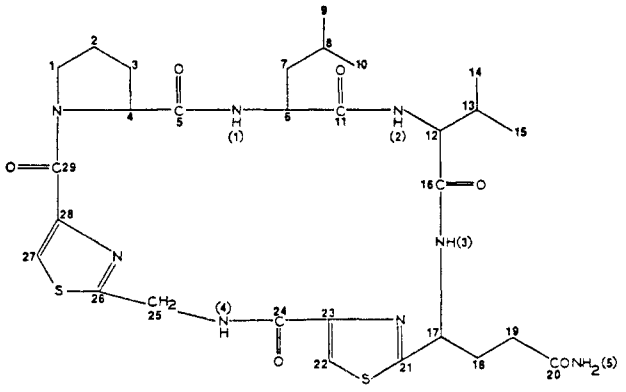
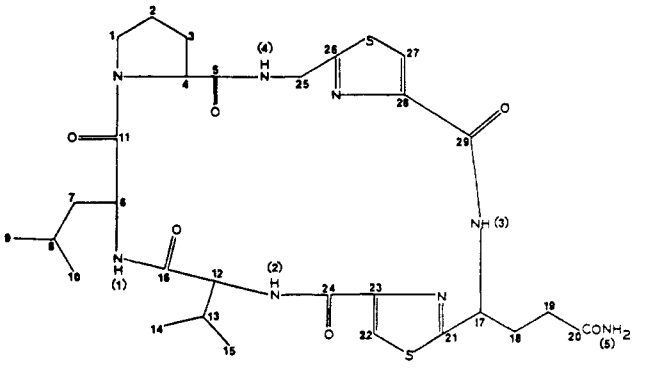
An all-L configuration reverse order of peptide bonding possibility for the cell growth inhibitory (PS system) cyclic peptide dolastatin 3 was eliminated by synthesis of thiazole amino acid containing peptide **2**. By employing a series (Scheme I) of mixed carbonic anhydride (except for **9** → **11** where DCCI–HBT was used) peptide bond forming reactions with *N*-Boc protection and a 2,4,5-trichlorophenol active ester cyclization step, cyclic pentapeptide **2** was obtained as a mixture of diastereomers corresponding to the (*R*)- and (*S*)-(gln)Thz unit. The thiazole amino acid components were synthesized employing a Hantzsch reaction as the key step (cf. Scheme II). Spectral analysis of the individual (*R*)- and (*S*)-(gln)Thz cyclic pentapeptide **2** removed both as structural candidates for dolastatin 3.

The Aplysiomorpha mollusc *Dolabella auricularia* has been found to contain a series of potent cell growth inhibitory (murine P388 lymphocytic leukemia, PS system) peptides designated dolastatins.[2] After an extensive series of isolation studies guided by bioassay (PS system) methods we were able to obtain nine of these potentially important substances in approximately 1-mg amounts. One of these, dolastatin 3, was subjected to detailed spectral and hydrolytic studies. On the basis of only 1 mg, dolastatin 3 was tentatively assigned structure **1**. As a



1, Cyclo[Pro-Leu-Val-(gln)Thz-(gly)Thz]

consequence of the limited supply and lack of crystallinity, two structural ambiguities remained unsettled. One question concerned the possibility of a reverse order of peptide bonding and the second the absolute configuration of the four chiral amino acids. Both possibilities became especially important when we synthesized (summary in preparation) the all-L isomers [with (*R*)- and (*S*)-(gln)Thz] corresponding to structure **1** and found it to be close to but not identical with dolastatin 3. Thus, in order to eliminate or confirm the reverse order of bonding for dolastatin 3 the synthesis of *cyclo*-[(gly)Thz-(*R* and *S*)-(gln)Thz-L-Val-L-Leu-L-Pro] (**2**) was undertaken. Synthesis of all 16 diastereomers of cyclic peptide **2** would require considerable effort. So we decided to concentrate on preparing the diastereomer possessing an all-L configuration in the Val-Leu-Pro segment. The overall synthetic strategy is briefly outlined in Scheme I.



2, Cyclo[(gly)Thz-R and S-(gln)Thz-L-Val-L-Leu-L-Pro]

Reaction of Boc-L-Leu with isobutyl chloroformate and *N*-methylmorpholine followed by L-Pro-OMe gave Boc-L-Leu-L-Pro-OMe (**3**) in 80% yield. Treatment of dipeptide **3** with ethereal hydrogen chloride gave (86%) L-Leu-L-Pro-OMe (**4**)·HCl[4] and this dipeptide was more conveniently prepared in 68% overall yield by eliminating chro-

(1) (a) Antineoplastic Agents and Structural Biochemistry series, contibutions 109 and 24, respectively. For parts 108 and 23, see: Holzapfel, C. W.; Pettit, G. R. *J. Org. Chem.*, submitted for publication. (b) Abstracted in part from the Ph.D. dissertation of PSN, submitted to the Graduate School, Arizonia State University, Tempe, May 1983.

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