min). After 30 h equilibrium was reached, the solvent was removed, and the reaction mixture was purified by HPLC (30% to 40% EtOAc/hexanes in 10 min) to afford 9α-hydroxy-*cis*-isotachysterol$_3$ (**20b**, 30%), (3*S*,9*S*,10*R*)-(*Z*,*Z*)-9,10-secocholesta-5,7,14-triene-3,9-diol (**21b**, 60%) and (3*S*,9*S*,10*S*)-(*Z*,*Z*)-9,10-secocholesta-5,7,14-triene-3,9-diol (**22b**, traces).

9α-Hydroxy-*cis*-isotachysterol$_3$ (20b): ^{1}H NMR δ 5.98 (2 H, AB system, J = 13 Hz, H6 and H7), 4.15 (1 H, s, H9), 3.91 (1 H, m, H3α), 1.57 (3 H, s, CH_3-C_{19}), 0.96 (3 H, d, J = 6.6 Hz, CH_3-C_{21}), 0.87 (3 H, s, CH_3-C_{18}), 0.87 (6 H, d, J = 6.6 Hz, CH_3-C_{26} and CH_3-C_{27}); ^{13}C NMR δ 151.6, 130.4, 130.3, 127.8, 127.4, 126.6, 67.0, 65.2, 55.7, 44.0, 39.5, 37.5, 35.8, 34.6, 31.7, 30.8, 29.6, 28.1, 28.0, 27.0, 26.4, 23.6, 22.7, 22.5, 19.8, 18.8, 16.8; IR (KBr) 3340 (OH, br), 2930 (CH, s), 2860 (CH, s), 1655 (w), 1465 (m), 1365 (m), 1040 (m), 1010 (m), 885 (w) cm^{-1}; UV (95% Et_2O) λ_{max} 215 (7400), 260 (8000); λ_{min} 227 nm (4900); LREIMS m/e (relative intensity) 400 (M^+, 10), 382 ($M^+ - H_2O$, 26), 367 ($M^+ - H_2O$–CH_3, 59), 364 ($M^+ - 2H_2O$, 12), 349 ($M^+ - 2H_2O - CH_3$, 34), 269 (M^+ - side chain - CH_3, 48), 251 (38), 209 (29), 197 (28), 195 (24), 183 (25), 169 (28), 157 (31), 155 (35), 143 (39), 131 (44), 129 (39), 119 (34), 105 (56), 91 (100), 81 (41), 79 (43); HREIMS calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3323.

(3*S*,9*S*,10*R*)-(*Z*,*Z*)-9,10-Secocholesta-5,7,14-triene-3,9-diol (21b): ^{1}H NMR δ 6.34 and 6.06 (AB, J = 11.5 Hz, 2 H, H6 and H7), 5.66 (dd, J = 3.1 and 1.8 Hz, 1 H, H15), 4.19 (s, 1 H, H9), 3.55 (m, 1 H, H3α), 3.05 (m, 1 H), 1.09 (d, J = 7.2 Hz, 3 H, CH_3-C_{19}), 0.95 (d, J = 6.2 Hz, 3 H, CH_3-C_{21}), 0.88 (d, J = 5.6 Hz, 6 H, CH_3-C_{26} and CH_3-C_{27}), 0.87 (s, 3 H, CH_3-C_{18}); UV (Et_2O) λ_{max} 273 nm; LREIMS m/e (relative intensity) 400 (M^+, 8), 382, ($M^+ - H_2O$, 57), 367 ($M^+ - H_2O - CH_3$, 34), 364 ($M^+ - 2H_2O$, 64), 349 ($M^+ - 2H_2O - CH_3$, 38), 269 (M^+ - side chain - CH_3, 40), 251 (50), 209 (29), 197 (29), 195 (23), 183 (22), 169 (24), 157 (31), 155 (29), 143 (36), 131 (37), 129 (38), 119 (27), 117 (23), 115 (21), 107 (26), 105 (44), 95 (40), 91 (43), 83 (43), 81 (57), 71 (53), 69 (100); HREIMS calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3342.

Thermolysis of 9α-Hydroxy-(7*E*)-vitamin D$_3$ (15) in Benzene. A solution of **15** (0.03 g, 0.078 mmol) in benzene (10 mL) was heated at 80 °C and monitored by HPLC analysis. After 3 h no starting material was observed. Concentration of the reaction mixture gave a residue that was purified by HPLC (30–40% EtOAc/hexanes in 10 min) to afford two products: 9α-hydroxy-*cis*-isotachysterol$_3$ (**20b**, 16 mg, 50%) and (3*S*,9*S*,10*S*)-(*Z*,*Z*)-9,10-secocholesta-5,7,14-treine-3,9-diol (**22b**, 3 mg, 10%).

(3*S*,9*S*,10*S*)-(*Z*,*Z*)-9,10-Secocholesta-5,7,14-triene-3,9-diol (22b): ^{1}H NMR δ 6.41 and 6.14 (2 H, AB system, J = 11.1 Hz, H6 and H7), 5.66 (1 H, dd, J = 3.1, 2.0 Hz, H15), 4.21 (1 H, s, H9), 4.07 (1 H, m, H3α), 3.05 (1 H, m, H10), 1.12 (3 H, d, J = 7.1 Hz, CH_3-C_{19}), 0.95 (3 H, d, J = 6.1 Hz, CH_3-C_{21}), 0.89 (3 H, s, CH_3-C_{18}), 0.87 (6 H, d, J = 6.5 Hz, CH_3-C_{26} and CH_3-C_{27}); UV (Et_2O) λ_{max} 273 nm; LREIMS m/e (relative intensity) 400 (M^+, 3), 382 ($M^+ - H_2O$, 10), 367 ($M^+ - H_2O - CH_3$, 10), 364 ($M^+ - 2H_2O$, 8), 349 ($M^+ - 2H_2O - CH_3$, 6), 269 (M^+ - side chain - CH_3, 10), 259 (11), 251 (9), 209 (6), 197 (7), 195 (5), 185 (9), 161 (25), 157 (10), 155 (9), 148 (25), 143 (11), 137 (12), 133 (14), 129 (23), 111 (26), 109 (18), 105 (17), 97 (40), 95 (30), 85 (36), 81 (40), 79 (14), 73 (40), 71 (59), 69 (100); HREIMS calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3336.

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Partial Synthesis of Sesquiterpene Lactones: A Route to 7,11-Ene-13-hydroxyeudesmanolides

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An efficient partial synthesis of several sesquiterpene lactones has been carried out from costunolide by treatment with trimethyl(phenyl)ammonium perbromide. A selective bromination at the C-11=C-13 bond provides a new route to 7,11-ene-13-hydroxyeudesmanolides. A synthesis of arbusculin D has been achieved.

In recent years, several cytotoxic and phytotoxic brominated sesquiterpenes have been reported.[1-3] As part of our research program on the synthesis of biologically active compounds, we have focused attention on the preparation of brominated sesquiterpene lactones.

We have recently reported that trimethyl(phenyl)ammonium perbromide (TMPAP) is an efficient reagent for bromocyclization of germacranolides.[4] This reaction, which can be extended to other cyclodecadiene systems,[5] can lead to the formation of specifically functionalized cyclized compounds that are valuable intermediates in the synthesis of sesquiterpenoids. We have also shown that TMPAP can be used effectively in bromine addition to conjugated double bonds, as in the case of α,β-unsaturated γ-lactones, thus providing a method for obtaining sesquiterpene lactones functionalized at the lactone ring.

This paper deals with the application of TMPAP to the partial synthesis of several sesquiterpene lactones.

Results and Discussion

Our approach was based on the cyclization of costunolide (1), a natural germacranolide readily available from natural sources.[5a] The cyclization of medium-ring 1,5-dienes has been widely investigated.[6-13] It has been demonstrated

(1) Barnekow, D. E.; Cardellina, J. H.; Zektzer, A. S.; Martin, G. E. *J. Am. Chem. Soc.* **1989**, *111*, 3511.
(2) Brennan, M. R.; Erickson, K. L. *J. Org. Chem.* **1982**, *47*, 3917.
(3) Rose, A. F.; Sims, J. J.; Wing, R. M.; Wiger, G. M. *Tetrahedron Lett.* **1978**, *2533-2536*.
(4) Collado, I. G.; Madero, J. G.; Massanet, G. M.; Luis, F. R. *Tetrahedron Lett.* **1990**, *31*, 563.
(5) Unpublished results. Semmler, F. W.; Feldstein, J. *Ber.* **1914**, *47*, 2687.
(6) Ruzicka, L. *Experientia* **1953**, *9*, 357.

0022-3263/91/1956-3587$02.50/0

Scheme I

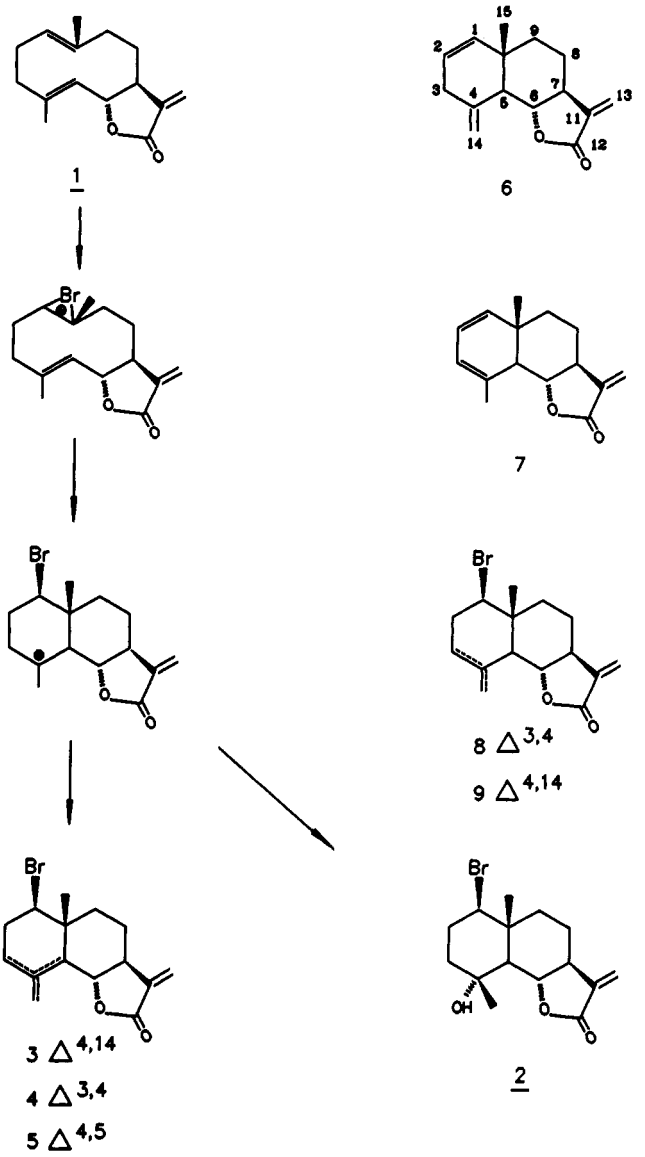
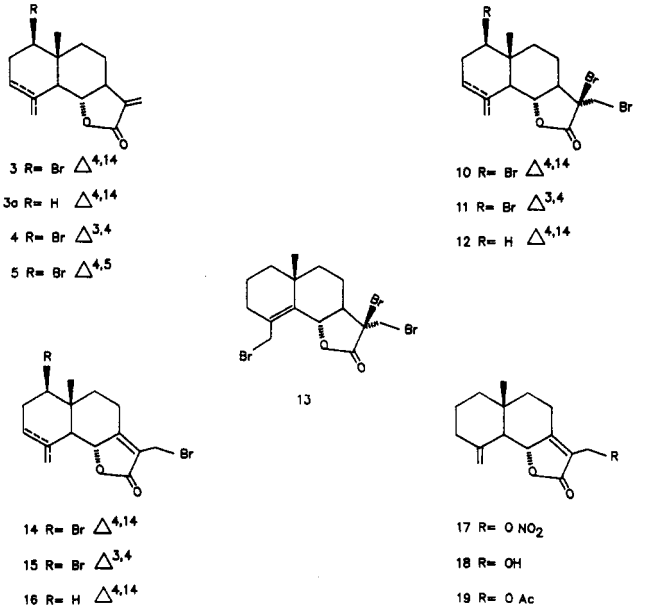


Chart I



that the course of carbocyclization depends largely, among other factors, upon the steric and conformational characteristics of the olefinic substrate, which are controlled by the polarity of the solvent employed. Thus, Jain et al.[14,15] employed *N*-bromosuccinimide for brominative cyclization, using a mixture of acetone/water as solvent, obtaining good yields of bromohydrins **2** and low yields of bromo lactones **3** and **4**.

The bromocyclization of costunolide (**1**) with TMPAP in the presence of a small amount of pyridine resulted in the formation of bromolactones **3–5** in 70, 20, and 5% yield, respectively (Scheme I). When a few drops of water were added to the reaction mixture, the bromo lactones **3–5** were accompanied by bromo lactone **2** in 20% yield.

When pure samples of bromo lactones **3** and **4** were refluxed in DMF with $LiBr/Li_2CO_3$, the eudesmanolides 3-deoxybrachylaenolide (**6**) and gazanolide[16] (**7**) were obtained in 90 and 87% yield, respectively (Scheme I). Compound **8** was obtained from **4** when the reaction mixture was heated 120 °C. This fact can be rationalized if we assume a nucleophilic displacement of the bromine atom at C-1 by the bromide anion. The enhancement of the nucleophilic character of Br^- in DMF can account for this transformation.

The corresponding epimer of bromolactone **3**, compound **9**, was detected by TLC but could not be isolated in sufficient amounts for unqualified characterization.

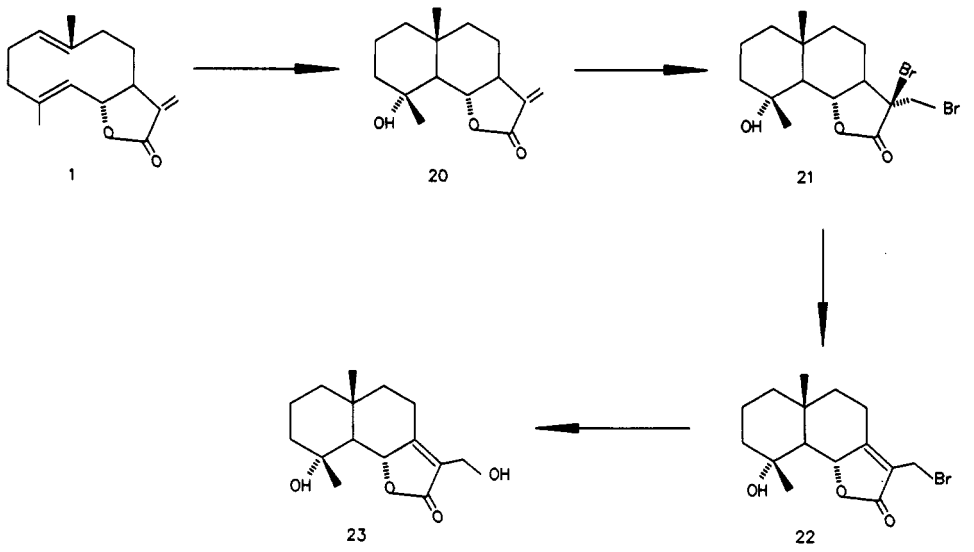
When bromocyclization was carried out without pyridine, tribromide **10** was detected. Furthermore, treatment of pure **3** and **4** with excess of TMPAP in dioxane afforded **10** and **11** in 78 and 71% yield, respectively (Chart I). Analysis of these products by ^1H NMR showed that addition of bromine to the C-11=C-13 bond had taken place. The paramagnetic shift for the H-6 signals (0.43 and 0.30 ppm) with respect to those for the same proton in **3** and **4** indicated a β-orientation for the bromine atom at C-11.

Although TMPAP has been used as a source of bromine for electrophilic addition to double bonds,[17,18] addition to the C-4=C-14 and C-3=C-4 bonds was not detected. Instead, bromine has added chemo- and stereospecifically to the double bond conjugated to the carbonyl group of the γ-lactone.

It may argued that the bromine at C-1 prevents the bromination at C-4=C-14 for stereoelectronic reasons. However, compound **3a**, on treatment with TMPAP under the previous conditions, yielded **12** (52%) and **13** (13%), thus indicating that the influence of the substituent at C-1 on the selectivity is very small. The tribromide **13** must be formed by further electrophilic addition at C-4=C-14 by molecular bromine, arising from the disproportion of Br_3^- to $Br_2 + Br^-$ followed by dehydrobromination.[19]

(7) Barton, D. H. R.; de Mayo, P. *J. Chem. Soc.* **1957**, *150*.
(8) Barton, D. H. R.; Bockman, O. C.; de Mayo, P. *J. Chem. Soc.* **1960**, *2263*.
(9) Allen, F. H.; Brown, E. D.; Rogers, D.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1967**, *1116*.
(10) Brown, E. D.; Solomon, M. D.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Chem. Commun.* **1967**, *111*.
(11) Sam, T. W.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1971**, *970*.
(12) Sutherland, J. K. *Tetrahedron* **1974**, *30*, 1651.
(13) Van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111.
(14) (a) Jain, T. C.; Banks, C. M.; McCloskey, J. E.; (b) *Tetrahedron.* **1979**, *35*, 885; (c) *Tetrahedron Lett.* **1970**, *2387*. (d) Jain, T. C.; Banks, C. M. *Can. J. Chem.* **1980**, *58*, 447.
(15) Jain, T. C.; McCloskey, J. E., *Tetrahedron Lett.* **1971**, *1415*.
(16) Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 332.
(17) Collado, I. G.; Fraga, B. M.; Hanson, J. H.; Hitchcock, P. B.; Tellado, F. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, *105*.
(18) Collado, I. G.; Fraga, B. M.; Hanson, J. H.; Hitchcock, P. B.; Tellado, F. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, *1451*.

Scheme II



The previous results show that reaction of TMPAP with a conjugated double bond is an intriguing reaction that involves stereoselective addition of bromine to the C-11=C-13 bond and can be explained as a nucleophilic 1,2 addition of bromine via initial attack of Br_3^- at C-13.[20]

This selective bromination provides a convenient access to several sesquiterpene lactones that possess a particular functionalization at the γ-lactone ring. In particular, 13-substituted sesquiterpene lactones possessing 7,11-unsaturation can be easily prepared from α-methylene γ-lactones using this methodology. Thus, treatment of compounds **10–12** with $LiBr/Li_2CO_3$ under mild conditions yielded the corresponding dehydrobrominated derivatives **14–16**.

The allylic bromine atom at C-13 can be easily substituted by other nucleophiles. Compounds **17** and **18** (98 and 75% yield, respectively) were obtained by treatment of **16** with freshly prepared $AgNO_3$ and Ag_2CO_3. Compound **18** formed a monoacetate **19** on acetylation with acetic anhydride/pyridine.

The applicability of these reactions was tested in the partial synthesis of arbusculin D (Scheme II), a sesquiterpene lactone with antifungal activity[22] isolated from *Artemisia arbuscula*.[21] Cyclization of costunolide (**1**) with *p*-toluenesulfonic acid in dioxane/water resulted in an improvement in the selective formation of the desired 4-hydroxyeudesmanolide arbusculin A[23] (**20**, 70%). Treatment of **20** with TMPAP afforded dibromide **21** (85%). Subsequent dehydrobromination gave **22** (95%). When monobromide **22** was treated with Ag_2CO_3, arbusculin D **23** was obtained in 70% yield.[21]

In conclusion, we have shown that the trimethyl(phenyl)ammonium perbromide is an excellent reagent for the partial synthesis of sesquiterpene lactones. In contrast to previous reports, the elimination of bromine at C-1 has been carried out and we have demonstrated that it occurs via epimerization. Furthermore, selective bromination of the C-11=C-13 double bond provides a route to sesquiterpene lactones functionalized in the γ-lactone ring, particularly to 7,11-ene-13-hydroxyeudesmanolides.

(19) Awang, D. V. C.; Wolfe, S. *Can. J. Chem.* **1969**, *707*.
(20) (a) Morton, I. D.; Robertson, P. W. *J. Chem. Soc.* **1945**, *129*. (b) De la Mare, P. B. D.; Robertson, P. W. *J. Chem. Soc.* **1945**, *888*.
(21) Irwin, M. A.; Geissman, T. A. *Phytochemistry* **1973**, *12*, 853.
(22) Pickman, A. K. *Biochem. Syst. Ecol.* **1984**, *12*, 13–18.
(23) Irwin, M. A.; Geissman, T. A. *Phytochemistry* **1969**, *2411*.

Experimental Section

Melting points are uncorrected. TLC analysis was carried out on silica gel (60 F_{254}, Merck, 0.063–0.200 mm). Spots were revealed by spraying with H_2SO_4/H_2O/AcOH (4:16:80) and heating at 100 °C.

(a) Cyclization of Costunolide (1) in Dioxane. A solution of costunolide (1; 500 mg) in dioxane (15 mL) was treated with TMPAP (875 mg) for 10 min at room temperature. Ether was added to precipitate the reagent, and the reaction mixture was then filtered and the solvent evaporated under reduced pressure. The residue was subjected to column chromatography (ethyl acetate/light petroleum (1:9), v/v) to yield **3** (150 mg), **4** (100 mg), **5** (30 mg), and **10** (20 mg).

(b) Cyclization of Costunolide (1) in Dioxane/Pyridine. A solution of costunolide (1; 500 mg) in dioxane/pyridine (15:2 mL) was treated with TMPAP (830 mg) for 15 min at room temperature to afford, after usual workup and chromatography with ethyl acetate/light petroleum (1:9), **3** (470 mg, 70%), **4** (134 mg, 20%), and **5** (34 mg, 5%).

(c) Cyclization of Costunolide (1) in Dioxane/H_2O/Pyridine. The reaction was repeated using dioxane (15 mL) to which H_2O (1 mL) and pyridine (2 mL) were added. The usual workup and column chromatography (ethyl acetate/light petroleum (3:7)) gave, in addition to compounds described in (b), **3** (335 mg, 50%), **4** (100 mg, 15%), **5** (14 mg, 2%), and the 4-hydroxylactone **2** (140 mg, 20%).

1β-Bromo-4α-hydroxycyclocostunolide (2): mp 187–188 °C (from petroleum ether/EtOAc); $[\alpha]_{589}$ +120° (*c* 1.0, $CHCl_3$); IR (film) 3525, 1764, 1665, 880 cm^{-1}; ^1H NMR ($CDCl_3$) 3.96 (dd, 1 H, $J_{1,2}$ = 4.6, 12.3 Hz, 1-H), 2.2–2.4 (m, 2 H, 3-H), 1.93 (d, 1 H, *J* = 11.1 Hz, 5-H), 4.07 (t, 1 H, *J* = 11.1 Hz, 6-H), 2.61 (ddd, 1 H, *J* = 11.1 Hz, 7-H), 6.11 (d, 1H, *J* = 3.0 Hz, 13-H), 5.45 (d, 1 H, *J* = 3.0 Hz, 13′-H), 1.35 (s, 3 H, 14-H), 1.09 (s, 3 H, 15-H); MS *m/e* (relative intensity) 313, 315 ($M^+ - CH_3$; 16.97; 16.00), 295:297 (16.73:15.98). Anal. Calcd for $C_{15}H_{21}O_3Br$: C, 54.71; H, 6.42. Found: C, 54.8; H, 6.4.

1β-Bromo-β-cyclocostunolide (3): mp 134–136 °C (from EtOAc); $[\alpha]_{589}$ +113° (*c* 1.06, $CHCl_3$); IR (KBr) 1765, 1645, 920 cm^{-1}; ^1H NMR ($CDCl_3$) 4.08 (d br, 1 H, *J* = 11 Hz, 1-H), 2.25 (d, 1 H, *J* = 10.6 Hz, 5-H), 3.94 (t, 1 H, *J* = 10.6 Hz, 6-H), 2.48 (ddd, 1 H, *J* = 10.6, 3 Hz, 7-H), 6.03 (d, 1 H, *J* = 3 Hz, 13-H), 5.36 (d, 1 H, *J* = 3 Hz, 13′-H), 4.94 (s br, 1 H, 14-H), 4.82 (s br, 1 H, 14′-H), 0.89 (s, 3 H, 15-H); MS *m/e* (relative intensity) 310:312 (M^+; 1.3:1.2), 295:297 ($M^+ - CH_3$; 9.1:9.0), 231 (M^+ - Br; 48.1). Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.15. Found: C, 57.79; H, 6.16.

1β-Bromo-α-cyclocostunolide (4): mp 111–113 °C (from EtOAc); $[\alpha]_{589}$ +50° (*c* 1.10, $CHCl_3$); IR (KBr) 1760, 1645, 880, 850 cm^{-1}; ^1H NMR ($CDCl_3$) 4.23 (dd, 1 H, *J* = 11.3, 7 Hz, 1-H), 2.55 (m, 2 H, 2-H, 2′-H), 5.26 (s br, 1 H, 3-H), 2.55 (m, 1 H, 5-H), 3.91 (t, 1 H, *J* = 11.2, 6-H), 2.11 (t br, 1 H, *J* = 11.2, 7-H), 6.06

(d, 1 H, J = 3.24, 13-H), 5.39 (d, 1 H, J = 3.24, 13'-H), 1.82 (s br, 3 H, 14-H), 0.97 (s, 3 H, 15-H); MS m/e (relative intensity) 310:312 (M^+; 1.35), 295:297 ($M^+ - CH_3$; 9.16:9.05), 231 ($M^+ - Br$; 49.5). Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.15. Found: C, 57.7; H, 6.10.

1β-Bromoarbusculin B (5): mp 131-132 °C (from EtOAc); $[\alpha]_{589}$ +57° (c 1.0, $CHCl_3$); IR (KBr) 1765, 1650, 880 cm^{-1}; ^1H NMR ($CDCl_3$) 4.10 (dd, 1 H, J = 4.12, 10.0 Hz, 1-H), 1.9–2.4 (m, 4 H, 2-H, 3-H), 4.47 (d br, 1 H, J = 10.2, 6-H), 2.53 (ddd, 1 H, J = 10.2, 3.2 Hz, 7-H); 1.55 (m, 1 H, 8-H); 1.22 (m, 1 H, 9-H), 6.10 (d, 1 H, J = 3.2 Hz, 13-H), 5.42 (d, 1 H, J = 3.2 Hz, 13'-H), 1.81 (s, 3 H, 14-H), 1.21 (s, 3 H, 15-H); MS m/e (relative intensity) 310:312 (M^+; 7:6.5), 295:297 ($M^+ - CH_3$; 17.5:18), 231 ($M^+ - Br$) (100). Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.15. Found: C, 57.65; H, 6.21.

Elimination of Bromine at C-1. The bromo lactone 4 (400 mg) was dissolved in dimethylformamide (10 mL), and LiBr (65 mg) and Li_2CO_3 (55 mg) were added. The mixture was heated 120 °C (no reflux) overnight. TLC revealed two clear spots. The reaction mixture was neutralized with aqueous acetic acid and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was washed with water, dried, and concentrated under reduced pressure. Chromatography (EtOAc/light petroleum (9:1)) afforded compounds 7 and 8 (40 and 45%, respectively). When the reaction was repeated under reflux for 180 min, gazanolide (7) was obtained in 87% yield.

Gazanolide (7): oil; IR (film) 2935, 1750, 1650, 780 cm^{-1}; ^1H NMR ($CDCl_3$) 5.51 (dd, 1 H, J = 10, 0.8 Hz, 1-H), 5.78 (dd, 1 H, J = 10, 5 Hz, 2-H), 5.68 (m, 1 H, 3-H), 2.65 (d br, 1 H, J = 10.5, 5-H), 3.99 (t, 1 H, J = 10.5, 6-H), 2.51 (t br, 1 H, J = 10.5, 7-H), 6.03 (d, 1 H, J = 3 Hz, 13-H), 5.38 (d, 1 H, J = 3 Hz, 13'-H), 1.96 (s br, 3 H, 14-H), 0.88 (s, 3 H, 15-H); MS m/e (relative intensity) 230 (M^+; 60); exact mass m/e calcd for $C_{15}H_{18}O_2$ 230.3073, found 230.3080.

1α-Bromo-α-cyclocostunolide (8): gum; IR (KBr) 2950, 1750, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 4.03 (d, 1 H, J = 5 Hz, 1-H); 2.85 (d br, 1 H, J = 10.8 Hz, 5-H), 3.90 (t, 1 H, J = 10.8 Hz, 6-H); 2.11 (t br, 1 H, J = 10.8 Hz, 7-H), 6.06 (d, 1 H, J = 3 Hz, 13-H), 5.38 (d, 1 H, J = 3 Hz, 13'-H), 1.89 (s br, 3 H, 14-H), 0.98 (s, 3 H, 15-H); MS m/e (relative intensity) 310:312 (M^+; 1.9:1.8), 295:297 (M^+ - 15; 2.5:2.4), 231 ($M^+ - Br$; 29.5). Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.88; H, 6.15. Found: C, 57.80; H, 6.18.

3-Deoxybrachylaenolide (6). A solution of bromo lactone 3 (30 mg) in dimethylformamide (10 mL) was treated with $LiBr/Li_2CO_3$ (55/45 mg). The mixture was refluxed for 180 min. The usual workup and chromatography described previously yielded 18 mg (90%) of compound 6: colorless gum; IR (film) 2940, 1760, 1650, 900, 860, 820 cm^{-1}; ^1H NMR ($CDCl_3$) 5.55 (s br, 2 H, 1-H, 2-H), 2.55 (d, 1 H, J = 11 Hz, 5-H), 4.07 (t, 1 H, J = 11 Hz, 6-H), 2.66 (m, 1 H, 7 H), 6.09 (d, 1 H, J = 3 Hz, 13-H), 5.41 (d, 1 H, J = 3 Hz, 13'-H), 5.06 (s br, 1 H, 14-H), 4.9 (s br, 1 H, 14'-H), 0.89 (s, 3 H, 15-H); MS m/e (relative intensity) 230 (M^+; 49.5); exact mass m/e calcd for $C_{15}H_{18}O_2$ 230.3073, found 230.3077.

Reaction of 3 and 4 with TMPAP. Compounds 3 (100 mg) and 4 (50 mg) were separately dissolved in dioxane, to each solution excess TMPAP (200 and 100 mg) was added, and the mixtures were stirred overnight at room temperature. Ether was added to precipitate the reagent, the reaction mixtures were then filtered, and the solvent was evaporated under reduced pressure. The residues were chromatographed on silica with ethyl acetate/light petroleum (2:8) to furnish 10 (78%) and 11 (71%), respectively.

1β,11β,13-Tribromo-β-cyclocostunolide (10): gum; IR (KBr) 1783, 1645, 898, 860 cm^{-1}; ^1H NMR ($CDCl_3$) 4.12 (dd, 1 H, J = 11, 4.2 Hz, 1-H), 2.45 (d br, 1 H, J = 10.2 Hz, 5-H), 4.37 (t, 1 H, J = 10.2 Hz, 6-H), 2.18 (ddd, 1 H, J = 10.2, 3.5 Hz, 7-H); 4.15 (d, 1 H, J = 11 Hz, H-13), 3.83 (d, 1 H, J = 11 Hz, 13'-H), 5.03 (s br, 1 H, 14-H); 4.86 (s br, 1 H, 14'-H), 0.98 (s, 3 H, 15-H); MS m/e (relative intensity) 389:391:393 ($M^+ - Br$; 2.5:7:2.6), 309:311 (M^+ - 2Br; 4.6:4.2), 231 (M^+ - 3Br; 31.5). Anal. Calcd for $C_{15}O_2H_{19}Br_3$: C, 38.49; H, 4.05. Found: C, 38.46; H, 4.10.

1β,11β,13-Tribromo-α-cyclocostunolide (11): yellow oil; IR ($CHCl_3$) 2970, 1790, 1650, 850 cm^{-1}; ^1H NMR ($CDCl_3$) 5.23 (s br, 1 H, 3-H); 4.20 (t, 1 H, J = 10 Hz, 6-H), 4.13 (dd, 1 H, J = 10.5, 4.5 Hz, 1-H), 4.10 (d, 1 H, J = 11 Hz, 13-H); 3.8 (d, 1 H, J = 11 Hz, 13'-H), 2.15 (ddd, 1 H, J = 10, 2.7 Hz, 7-H), 1.80 (s br, 3 H, 14-H), 0.96 (s, 3 H, 15-H). Anal. Calcd for $C_{15}O_2H_{19}Br_3$: C, 38.49; H, 4.05. Found: C, 38.52; H, 4.12.

11β,13-Dibromo-β-cyclocostunolide (12) and 11β,13,14-Tribromoarbusculin B (13). TMPAP (167 mg, 0.43 mmol) was added to a stirred solution of **3a** (100 mg, 0.43 mmol) in dioxane (10 mL). After 60 min, more TMPAP (75.2 mg, 0.2 mmol) was added over about 30 min. The mixture was stirred for 120 min. The usual workup, described previously, and chromatography on silica gel with ethyl acetate/light petroleum (2:8) afforded 12 (52%) and 13 (13%). Dibromo derivative (12) had the following properties: IR ($CHCl_3$) 2940, 1790, 1650, 850 cm^{-1}; ^1H NMR ($CDCl_3$) 4.85 (s br, 1 H, 14-H), 4.66 (s br, 1 H, 14'-H), 4.22 (dd, 1 H, J = 10 Hz, 6-H), 4.05 (d, 1 H, J = 10.7, 13-H), 3.72 (d, 1 H, J = 10.7, 13'-H), 0.8 (s, 3 H, 15-H). Anal. Calcd for $C_{15}O_2H_{20}Br_2$: C, 45.9; H, 5.1. Found: C, 45.7; H, 5.5.

11β,13,14-Tribromoarbusculin B (13): yellow oil: IR (film) 2950, 1880, 870, 810 cm^{-1}; ^1H NMR ($CDCl_3$) 4.90 (d, 1 H, J = 10.5, 6-H), 4.3 (d, 1 H, J = 9.2 Hz, 14-H), 4.05 (d, 1 H, J = 9.2 Hz, 14'-H), 4.1 (d, 1 H, J = 10.5 Hz, 13-H), 4.75 (d, 1 H, J = 10.5 Hz, 13'-H), 2.20 (m, 2 H, 8-H), 1.10 (s, 3 H, 15-H); MS m/e (relative intensity) 389:391:393 ($M^+ - Br$; 39:76:38). Anal. Calcd for $C_{15}H_{19}O_2Br_3$: C, 38.49; H, 4.05. Found: C, 38.51; H, 4.11.

1β,13-Dibromo-7,11-ene-β-cyclocostunolide (14), 1β,13-Dibromo-7,11-ene-α-cyclocostunolide (15), and 13-Bromo-7,11-ene-β-cyclocostunolide (16). Elimination of the β-oriented bromine atom at C-11 was carried out for compounds 11–13 (100 mg) dissolved in DMF (20 mL) by treatment with $LiBr/Li_2CO_3$ (175:150 mg). The reaction mixture was heated to 60 °C for 2 h. The usual workup yielded after chromatography on silica gel (1.5:8.5) 14 (80%), 15 (75%), and 16 (90%), respectively.

1β,13-Dibromo-7,11-ene-β-cyclocostunolide (14): yellow gum; IR (film) 2940, 1745, 1660, 1640, 880 cm^{-1}; ^1H NMR ($CDCl_3$) 3.98 (dd, 1 H, J = 11.3, 4.5 Hz, 1-H), 2.0–2.5 (m, 2 H, H-2, H-2'), 1.90 (d, br, 1 H, J = 10.5 Hz, 5-H), 4.98 (d, 1 H, J = 10.5 Hz, 6-H), 4.07 (s, 2 H, H-13), 5.06 (s br, 1 H, 14-H), 4.98 (s, 1 H, 14'-H), 1.04 (s, 3 H, H-15); MS m/e (M^+) 388:390:391 (4:7:5), 309:311 (M^+ - Br; 100:96), 229 (M^+ - Br - BrH; 87). Anal. Calcd for $C_{15}H_{18}O_2Br_2$: C, 46.16; H, 4.65. Found: C, 46.20; H, 4.70.

1β,13-Dibromo-7,11-ene-α-cyclocostunolide (15): yellow gum; IR (film) 2950, 1750, 1660, 850 cm^{-1}; ^1H NMR ($CDCl_3$) 3.97 (m, 1 H, 1-H), 5.15 (m, 1 H, H-3), 4.7 (d, 1 H, J = 10.5 Hz, H-6), 4.1 (s, 2 H, 13-H, 13'-H), 1.82 (s br, 3 H, 14-H), 1.06 (s, 3 H, 15-H). Anal. Calcd for $C_{15}H_{18}O_2Br_2$: C, 46.16; H, 4.65. Found: C, 46.20; H, 4.70.

13-Bromo-7,11-ene-β-cyclocostunolide (16): colorless gum; IR (film) 2950, 1745, 1660, 880, 850 cm^{-1}; ^1H NMR ($CDCl_3$) 4.85 (d, 1 H, J = 9 Hz, 6-H); 2.82 (ddd, 1 H, J = 12, 5, 2 Hz, 8-H), 2.43 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 2.3 (d br, 1 H, J = 12 Hz, 9-H); 4.03 (s, 2 H, 13-H); 4.83 (s br, 1 H, 14-H); 4.93 (s br, 1 H, 14'-H), 0.87 (s, 3 H, 15-H); MS m/e (relative intensity) 310:312 (M^+;-1:90:1.7); 231 ($M^+ - Br$; 34). Anal. Calcd for $C_{15}H_{19}O_2Br$: C, 57.87; H, 6.16. Found: C, 57.82; H, 6.14.

13-Nitro-7,11-ene-β-cyclocostunolide (17). To a stirred solution of compound 16 (60 mg) in 15 mL of dioxane was added silica gel impregnated with 20% $AgNO_3$ (100 mg). The reaction mixture was stirred at room temperature for 60 min and then filtered on Celite and concentrated under reduced pressure. The crude product was chromatographed on silica gel (4:1 petroleum ether/EtOAc) to furnish pure nitro derivative 17 (55 mg, 98%): gum; IR (KBr) 1750, 1670, 1595, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) 5.1 (s, 2 H, 13-H); 4.97 (s br, 1 H, 14-H); 4.84 (s br, 1 H, 14'-H), 4.87 (d, 1 H, J = 10 Hz, 6-H), 2.92 (ddd, 1 H, J = 12, 5, 2 Hz, 8-H), 2.52 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 1.8 (d, 1 H, J = 10 Hz, 5-H), 0.89 (s, 3 H, 15-H). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.5. Found: C, 61.1; H, 6.0.

13-Hydroxy-7,11-ene-β-cyclocostunolide (18). To a stirred solution of 16 (100 mg) in dioxane/H_2O ((1:5), 16 mL) was added freshly prepared[24] Ag_2CO_3 (500 mg). After addition of Ag_2CO_3, the reaction mixture was stirred and heated to 60 °C for 2 d, and then it was washed successively with 3.5% aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and brine (20 mL). The

(24) The Ag_2CO_3 was obtained when a solution of $AgNO_3$ (680 mg) in water (10 mL) was poured in a aqueous solution (10 mL) of Na_2CO_3 (220 mg). The precipitate was filtered and dried with suction.

organic layer was dried and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel (1:1 petroleum ether/EtOAc) to give 60 mg (75%) of pure hydroxy derivative 18: gum; IR ($CHCl_3$) 3450, 1740, 1670, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 4.93 (s br, 1 H, 14-H), 4.84 (s br, 1 H, 14'-H), 4.84 (d, 1 H, J = 11 Hz, 6-H), 4.3 (s, 2 H, 13-H, 13'-H), 2.80 (ddd, 1 H, J = 12, 5, 2 Hz, 8-H); 2.39 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 0.87 (s, 3 H, 15-H); MS m/e (relative intensity) 248 (M^+; 17), 230 (M^+ - 18; 87). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.5; H, 8.12. Found: C, 72.1; H, 8.17.

13-Acetoxy-7,11-ene-β-cyclocostunolide (19). A solution of 18 (50 mg) in pyridine (2 mL) was treated with acetic anhydride (5 mL) for 24 h. The usual workup and chromatography give 19 (45 mg): gum; IR (film) 1740, 1660, 880 cm^{-1}; ^1H NMR ($CDCl_3$) 4.93 (s br, 1 H, 14-H), 4.83 (s br, 1 H, 14'-H), 4.72 (s, 2 H, 13-H, 13'-H), 4.84 (d, 1 H, J = 11 Hz, 6-H), 2.90 (d br, 1 H, J = 12 Hz, 8-H), 2.40 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 0.87 (s, 3 H, 15-H), 1.99 (s, 3 H, CH_3COO); MS m/e (relative intensity) 291 (M^+ + 1; 8), 230 (M^+ - 60; 73).

Arbusculin A (20): mp 77-78 °C in agreement with these reported in the literature;[28] IR (KBr) 3480, 1770, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 6.02 (d, 1 H, J = 3.0 Hz, 13-H), 5.36 (d, 1 H, J = 3.0 Hz, 13'-H), 3.92 (t, 1 H, J = 11 Hz, 6-H), 2.97 (s br, 1 H, CHO*H*), 2.6 (t br, 1 H, J = 11 Hz, 7-H), 1.76 (d, 1 H, J = 11 Hz, 5-H), 1.27 (s, 3 H, 14-H), 0.90 (s, 3 H, 15-H); MS m/e (relative intensity) 251 (M^+ + 1; 4.0), 235 (M^+ - 15; 7.2). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.07; H, 8.90.

11β,13-Dibromoarbusculin A (21). Arbusculin A (20; 100 mg) was dissolved in dioxane, TMPAP (200 mg) was added, and the mixture was stirred overnight at room temperature. After workup described for 10, chromatography afforded 21 (85%): gum; IR (KBr) 3450, 2950, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) 4.41 (dd, 1 H, J = 11, 9.7 Hz, 6-H), 4.16 (d, 1 H, J = 11 Hz, 13-H), 3.84 (d, 1 H, J = 11 Hz, 13'-H), 2.41 (ddd, 1 H, J = 9.7, 4.5 Hz, 7-H), 1.87 (d, 1 H, J = 11 Hz, 5-H), 1.37 (s, 3 H, 14-H), 1.01 (s, 3 H, 15-H). Anal. Calcd for $C_{15}H_{22}O_3Br_2$: C, 43.90; H, 5.41. Found: C, 43.86; H, 5.28.

13-Bromo-7,11-enearbusculin A (22). Compound 21 (100 mg) was dissolved in DMF (10 mL) and treated with $LiBr/Li_2CO_3$ (175:150 mg) as described before for 14. Chromatography (ethyl acetate/light petroleum (3:7)) gave 22 (95%): yellow gum; IR (KBr) 3480, 2970, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) 4.85 (d, 1 H, J = 9.8, 6-H), 4.0 (s br, 2 H, 13-H, 13'-H), 2.82 (dd, 1 H, J = 12, 5 Hz, 8-H), 2.4 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 1.47 (d, 1 H, J = 9.8 Hz, 5-H), 1.32 (s, 3 H, 14-H), 0.99 (s, 3 H, 15-H).

Arbusculin D (23). Compound 22 (100 mg) dissolved in dioxane/H_2O ((1:0.5), 10 mL) was treated with Ag_2CO_3 as described for 18, obtaining after chromatography on silica gel (1:1 petroleum ether/EtOAc) 23 (70%): mp 171-172 °C in agreement with those reported in the literature;[21] ^1H NMR ($CDCl_3$) 4.88 (d, 1 H, J = 11 Hz, 6-H), 4.30 (s br, 2 H, 13-H, 13'-H), 2.86 (dd, 1 H, J = 12, 5 Hz, 8-H), 2.42 (ddd, 1 H, J = 12, 5 Hz, 8'-H), 1.43 (d, 1 H, J = 11 Hz, 5-H) 1.33 (s, 3 H, 14-H), 0.99 (s, 3 H, 15-H) 3.20 (s br, 1 H, C-4-O*H*), 2.7 (m, 1 H, C-13-O*H*); MS m/e (relative intensity) 266 (M^+; 1.5), 251 (M^+ - 15; 12), 248 (M^+ - 18; 5), 230 (M^+ - 2×18; 9). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.78; H, 8.43.

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Synthesis of L-3'-Azido-3'-deoxythymidine and Its Stereoisomers

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We report the first synthesis of the L isomer of 3'-azido-3'-deoxythymidine (L-AZT). L-Arabinose was used as starting material for preparation of appropriately protected α,β-unsaturated aldehyde 5. Michael-type addition of azide to 5 gave 3-azido-2,3-dideoxypentofuranoses 7 and 8 suitable for nucleoside coupling with silylated thymine to afford after deprotection L-AZT (11), 1-(3-azido,-2,3-dideoxy-α-L-*erythro*-pentofuranosyl)thymine (12), 1-(3-azido-2,3-dideoxy-β-L-*threo*-pentofuranosyl)thymine (13) and 1-(3-azido-2,3-dideoxy-α-L-*threo*-pentofuranosyl)thymine (14). Anti-HIV activity of L-AZT is discussed.

Introduction

In the treatment of AIDS blocking, one or more steps of the replicative cycle of the human immunodeficiency virus (HIV) is a possible chemotherapeutic strategy.[1,2] Thus, different 2',3'-dideoxy nucleosides have turned out to be promising antiviral agents against AIDS, acting as inhibitors of the retrovirus reverse transcriptase.[1,3-5] Among the 2',3'-dideoxynucleosides, 3'-azido-3'-deoxythymidine (AZT) is very potent in its antiviral action, and at the present time it is the most successful agent used in the treatment of patients with AIDS.[1,5,6] But still there is an urgent need for new compounds with improved potency and selectivity in their antiviral action. Therefore, we decided to prepare the L isomer of 3'-azido-3'-deoxythymidine 11 (L-AZT) with special reference to testing this new mirror image of AZT against AIDS, having in mind that two enantiomeric forms of a biologically active compound often show differences in action and selectivity.

Results and Discussion

Originally, AZT was synthesized by Horwitz et al. from thymidine.[7] Recently, AZT has been prepared in multistep syntheses via 3-azido-2,3-dideoxypentoses from D-xylose[8] and D-mannitol.[9]

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(1) Mitsuya, H.; Broder, S. *Nature* **1987**, *325*, 773.
(2) De Clercq, E. *TIPS* **1987**, *8*, 339.
(3) De Clercq, E. *J. Med. Chem.* **1986**, *29*, 1561.
(4) Matthes, E.; Lehmann, Ch.; Scholz, D.; von Janta-Lipinski, M.; Gaertner, K.; Rosenthal, H. A.; Langen, P. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 78.
(5) Ono, K.; Ogaswara, M.; Iwata, Y.; Nakane, H.; Fujii, T.; Sawai, K.; Saneyoshi, M. *Biochem. Biophys. Res. Commun.* **1986**, *140*, 498.
(6) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
(7) Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076.

0022-3263/91/1956-3591$02.50/0