An Efficient, Enantioselective Synthesis of the Taxol Side Chain

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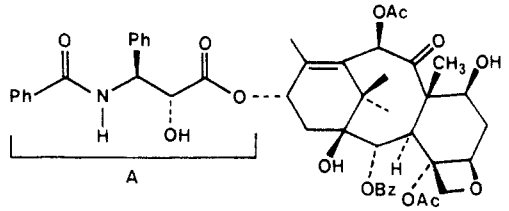
An asymmetric epoxidation (76–80% ee) and a highly regioselective epoxide cleavage have been used as the key reactions in the synthesis of the taxol side chain methyl ester (**2**; ≥95% ee, 23% overall yield from phenylacetylene). Transesterifications of **2** (in four steps) have been effected and are exemplified with (−)-isopinocampheol (**8**), 1,2;3,4-di-*O*-isopropylidene-D-galactopyranose (**9**), and methyl gibberellate (**10**).

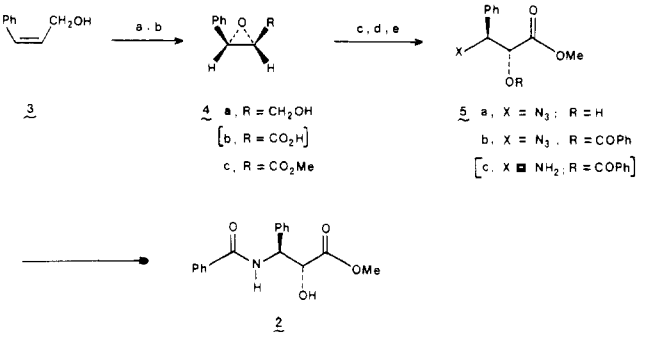
Taxol (**1**), a diterpene of the taxane group,[1] has been isolated from several species of the *Taxus* genus (Taxaceae family).[2] The unusually potent antileukemic and tumor



Taxol (**1**)

inhibitory properties of taxol[2,3] combined with its highly challenging structure have served to stimulate recently in a number of laboratories considerable synthetic activity,[4] much of which is apparently aimed at its eventual total synthesis. In the context of a more modest, but potentially quite rewarding, program directed toward a partial synthesis of taxol as well as the preparation of some analogues of taxol,[5] we have developed a highly efficient synthesis of the taxol side chain (A, methyl ester = **2**).[6] In this paper we describe this synthesis and the synthesis of several ester analogues.

Scheme I[a]



[a] Key: (a) *t*-BuOOH, Ti(O-*i*-Pr)$_4$, L-(+)-DET, −30 °C; (b) $RuCl_3$, $NaIO_4$, $NaHCO_3$; H^+; CH_2N_2; (c) Me_3SiN_3, $ZnCl_2$, 70 °C; H^+; (d) PhCOCl, Et_3N, DMAP; (e) H_2, 10% Pd-C; 72 h.

Discussion

The nature of the threo substituents on the taxol side chain (A) and the desire to obtain the final products in high optical purity (without having to resort to the separation of diastereomers) suggested an approach based on an asymmetric epoxidation[7] of *cis*-cinnamyl alcohol followed by a regioselective cleavage of the epoxide by a nitrogen nucleophile.[8] The ultimately successful synthesis based on this approach is shown in Scheme I.

cis-Cinnamyl alcohol (**3**), easily obtained from phenylacetylene in 88% yield by hydroxymethylation followed by Lindlar reduction,[9] was subjected to the titanium-catalyzed asymmetric epoxidation process.[7] The best results were obtained by running the reaction at −30 to −33 °C for 5–6 days, which yielded the desired (2*S*,3*R*)-epoxy alcohol **4a** in 61–65% yield and with an enantiomeric excess of 76–80%[10] over several runs. It was expected that several of the subsequent products would be nicely crystalline and thus would probably afford the opportunity to remove easily the minor amount (10–12%) of enantiomeric material.

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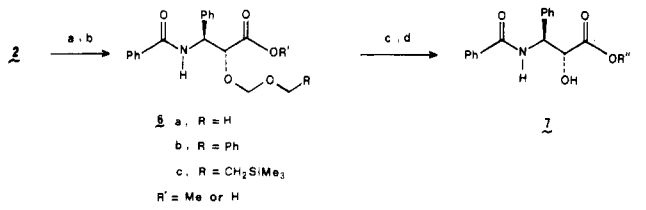
Scheme II[a]



[a] Key: (a) $ClCH_2OCH_2R$, $(i\text{-}Pr)_2NEt$; (b) K_2CO_3, $MeOH\text{-}H_2O$; (c) R''OH, 2-DPC or DCC, DMAP; (d) Me_3SiBr, 4 Å molecular sieves (R = H), H_2-Pd (R = Ph), or aqueous HF-MeCN (R = CH_2SiMe_3).

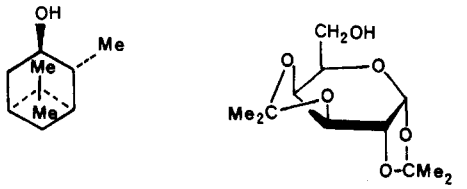
In order to avoid protecting group related manipulations, epoxy alcohol **4a** was oxidized prior to the epoxide cleavage. While this oxidation could be accomplished by using a catalytic amount of platinum under an oxygen atmosphere,[11] a much more satisfactory procedure involved the use of ruthenium trichloride–sodium periodate.[12] Because of the observed relative instability of the resultant free acid **4b**, the reaction product, without isolation, was routinely converted to the methyl ester **4c**[13] with ethereal diazomethane (84% yield). Not surprisingly, both oxidation reactions were much higher, yielding, when run in the presence of a few equivalents of sodium bicarbonate, which served to stabilize the acid as it formed as its sodium salt.

The next hurdle to be surmounted was the epoxide cleavage. We were most concerned about a possible lack of regioselectivity, a problem that frequently plagues this type of reaction.[8,14] Thus, we were delighted to find that azidotrimethylsilane and a catalytic amount of zinc chloride[15]—a combination that has rarely been used for this purpose—served to transform the epoxide **4c** exclusively (NMR, TLC) to the desired hydroxy azide **5a** (obtained after in situ acid hydrolysis in 90% yield). In light of the reported[15] selective conversion of styrene oxide to 2-azido-1-phenylethanol under these conditions, the above result **4c** → **5a** suggests that there are both steric and electronic effects operative in this reaction.

An O → N benzoyl transfer[16] was now used effectively to obtain the taxol side chain methyl ester (**2**). Azido benzoate **5b**, prepared from **5a** as indicated in 94% yield, was hydrogenated in methanol to produce the amino benzoate **5c**, which, in turn, conveniently rearranged in situ to give the desired product **2** in 89% yield. A single recrystallization of **2** from chloroform then afforded the *optically pure* (≥95%)[10a] *material in 23% overall yield from phenylacetylene.* A comparison of the melting point (mp 184–185 °C; lit.[2a,b] mp 183–185 °C, 184–185 °C), optical rotation ($[\alpha]_D$ −48°; lit.[2a] $[\alpha]_D$ −49.6°), and spectral data for **2** with the literature values[2] fully confirmed its identity.

We have used this readily available product for the synthesis of a variety of ester analogues **7**, as shown in Scheme II.

Remarkably little latitude existed in the choice of the hydroxyl protecting group(s) for **2**. Not only did the usual problems of introduction and removal under conditions compatible with diverse functional groups have to be considered, but also did the potential difficulty of having an adjacent (acidic) carboxyl group;[17] in addition, the tendency of certain protecting groups to promote C-2 epimerization in similar molecules needed to be taken into account.[18] After considerable trial and error, the methoxymethyl and substituted methoxymethyl groups (R = H, Ph, CH_2SiMe_3)[19] were found to be well suited and, taken together, to allow the greatest degree of flexibility. Esters **6a–c (R′ = CH_3)** so protected were readily hydrolyzed to the corresponding free acids (R′ = H), which could then be reesterified with a variety of alcohols in generally fair to excellent yields by using either the recently described, excellent procedure involving 2-dipyridyl carbonate (2-DPC) and 4-(dimethylamino)pyridine (DMAP)[20] or that employing dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine.[21] In no case were any diastereomeric products detected.[18] Deprotection of these esters with the appropriate, selective reagent (Me_3SiBr, H_2–Pd, HF)[19] then afforded the desired ester analogues **7**. The esterification–deprotections **6a–c (R′ = H)** → **7**, where R″OH is (−)-isopinocampheol (**8**, 64%), 1,2;3,4-di-*O*-isopropylidene-D-galactopyranose (**9**, 86%), and methyl gibberellate (**10**, C-3 OH, 43%), are fairly representative and are detailed in the Experimental Section.



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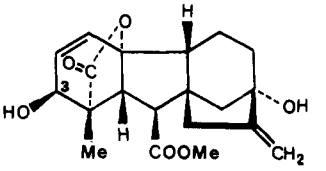

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The results described in this paper should find application in efforts directed toward the synthesis of taxol. We are currently examining the possibility of effecting a partial synthesis of taxol from 10-desacetyl baccatin III, a sub-

(11) See: Heynes, K.; Paulsen, H. In "New Methods of Preparative Organic Chemistry"; Foerst, W., Kirchner, F. K., Eds.; Academic Press: New York, 1963; Vol. II, pp 303–359.

(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. The oxidation of such epoxy alcohols is not trivial. See, for example: Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242–5244. Roush, W. R.; Blizzard, T. A. *Ibid.* **1984**, *49*, 4332–4339 and reference 18.

(13) Roux-Schmitt, M.-C.; Seyden-Penne, J.; Wolfe, S. *Tetrahedron* **1972**, *28*, 4965–4979 (racemic). The optically active methyl ester **4c** was also obtained, however much less efficiently, through resolution of the free acid **4b**.[14] The absolute stereochemistry of **4c** could be confirmed[7] by hydrogenation (5% Pd–C, EtOH, 23 °C) of a sample to give (*R*)-(+)-methyl 2-hydroxy-3-phenylpropionate. See: Verbit, L.; Heffron, P. J. *Tetrahedron* **1968**, *24*, 1231–1236.

(14) See: Harada, K. *J. Org. Chem.* **1966**, *31*, 1407–1410 and references cited therein. For recent work on this problem, see: Caron, M.; Sharpless, K. B. *Ibid.* **1985**, *50*, 1557–1560. Chong, J. M.; Sharpless, K. B. *Ibid.* **1985**, *50*, 1560–1563.

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(17) See, for example: Begley, M. J.; Cameron, A. G.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1984**, 827–829.

(18) See: Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 744–754.

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stance that is quite easily isolated relative to taxol.[2,22]

Experimental Section

Solvents were generally distilled prior to use. Tetrahydrofuran and ether were distilled from sodium hydride–lithium aluminum hydride, and amines and toluene were distilled from calcium hydride.

Reaction mixtures were generally stirred under a nitrogen or argon atmosphere. Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 70–230 silica gel 60 was employed for column chromatography. Melting points were obtained by using a Büchi-Tottoli apparatus and are not corrected.

3-Phenyl-2-propyn-1-ol. A stirred solution of 21.4 g (210 mmol) of phenylacetylene in 100 mL of tetrahydrofuran at −78 °C was treated dropwise with 125 mL (200 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After 2 h, the reaction mixture was allowed to warm to 0 °C, and then 12 g (400 mmol) of paraformaldehyde was added. After being stirred for 5 min at 0 °C and 2.5 h at 20 °C, the mixture was hydrolyzed and the reaction product was isolated with ether in the usual manner and distilled to give 25.3 g (91%) of 3-phenyl-2-propyn-1-ol:[9] bp 75–76 °C (0.06 torr); IR (neat) 3300, 3070, 3045, 2900, 2850, 2225, 1590, 1480, 1435, 1030, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (s, 1 H), 4.49 (s, 2 H), 7.15–7.60 (m, 5 H).

(*Z*)-3-Phenyl-2-propen-1-ol (3). A 46.1-g (349 mmol) sample of 3-phenyl-2-propyn-1-ol, 9.22 g of Lindlar catalyst (Fluka), and 0.171 g of Lindlar catalyst poison (Fluka)[9] were vigorously stirred in 185 mL of toluene at 20 °C under a hydrogen atmosphere. Upon completion of the reaction (18 h, TLC), the mixture was filtered, and the toluene was removed under reduced pressure. Distillation of the residue then yielded 45.3 g (97%) of allylic alcohol 3:[9] bp 92–94 °C (0.2 torr); IR (neat) 3300, 3075, 3050, 3020, 2925, 2875, 1950, 1880, 1800, 1750, 1600, 1570, 1490, 1450, 1020, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (br s, 1 H), 4.41 (dd, J = 1.2 Hz, 6.3 Hz, 2 H), 5.70–6.00 (m, 1 H), 6.56 (br d, J = 11.7 Hz, 1 H), 7.02–7.45 (m, 5 H).

(2*S*,3*R*)-(−)-Phenyloxiranemethanol (4a). A stirred solution of 6.57 mL (6.27 g, 22.1 mmol) of titanium(IV) isopropoxide in 200 mL of methylene chloride at −23 °C was treated with a solution of 5.46 g (26.5 mmol) of diethyl L-tartrate in 10 mL of methylene chloride. After 5 min, 2.96 g (22.1 mmol) of allylic alcohol **3** in 10 mL of methylene chloride and 11.76 mL (44.2 mmol) of a 3.76 M solution of *tert*-butyl hydroperoxide in toluene were added, and the resulting solution was left for 5 days at −30 °C.[7] The solution was then treated with stirring at −23 °C with 55 mL of 10% aqueous tartaric acid. After being stirred for 0.5 h at −23 °C and 1 h at 20 °C, the reaction mixture was thoroughly extracted with methylene chloride, which was then dried over sodium sulfate. The residue obtained on evaporation of the solvents was dissolved in 165 mL of ether, and the resulting solution was treated at 0 °C with 66 mL of 1 N aqueous sodium hydroxide. After being stirred for 30 min at 0 °C, the reaction mixture was processed in the usual fashion and the resulting crude product was purified by dry silica gel chromatography with 40% ether in hexane and then by evaporative distillation (ca. 50 °C at 0.01 torr) to give 2.03 g (61%) of epoxy alcohol **4a**: $[\alpha]^{25}_D$ −50° (*c* 3.3, chloroform); IR (neat) 3400, 3075, 3050, 3020, 2970, 2920, 2860, 1950, 1880, 1810, 1740, 1600, 1490, 1450, 1198, 1040, 890, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (br s, 1 H), 3.3–3.6 (m, 3 H), 4.17 (d, J = 3 Hz, 1 H), 7.31 (br s, 5 H); mass spectrum, m/e 150 (M^+).

Samples of optically active **4a** and racemic **4a** were individually esterified in carbon tetrachloride–pyridine with the acid chloride from (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Fluka). The ^1H NMR spectrum (recorded in $CDCl_3$ with added $Eu(fod)_3$) of the Mosher ester from racemic **4a** displayed two sets of OCH_3 signals separated by 0.14 ppm; the corresponding ester from optically active **4a** under the same conditions showed the same signals but in a ratio of 89 (upfield):11 (downfield).[10]

(2*R*,3*R*)-(+)-Methyl 3-Phenyloxiranecarboxylate (4c). To a vigorously stirred mixture of 1.97 g (13.1 mmol) of the above epoxy alcohol **4a**, 5.50 g (65.5 mmol) of sodium bicarbonate, and 8.41 g (39.3 mmol) of sodium periodate in 26.2 mL of carbon tetrachloride, 26.2 mL of acetonitrile, and 39.3 mL of water was added 98.5 mg (0.38 mmol) of ruthenium trichloride trihydrate.[12] The mixture was stirred at 20 °C for 44 h, after which the acidic material was extracted at 0 °C carefully into ether, which was dried briefly over sodium sulfate, and then treated for 15 min with excess ethereal diazomethane. The residue obtained on evaporation of the solvents was purified by dry-column chromatography with 10% ether in hexane to afford 1.97 g (84%) of epoxy ester **4c**:[13] $[\alpha]^{25}_D$ +11° (*c* 4.4, chloroform); IR (neat) 3075, 3060, 3020, 2990, 2950, 1750, 1435, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.52 (s, 3 H), 3.81 (d, J = 4.7 Hz, 1 H), 4.24 (d, J = 4.7 Hz, 1 H), 7.16–7.54 (m, 5 H); mass spectrum, m/e 178 (M^+). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.40; H, 5.60.

(2*R*,3*S*)-(+)-Methyl 3-Azido-2-hydroxy-3-phenylpropionate (5a). A 1.95-g (10.94 mmol) sample of the above epoxy ester **4c**, 1.51 g (13.11 mmol) of azidotrimethylsilane, and 58 mg (0.43 mmol) of zinc chloride were stirred at 68 °C for 15 h at which time an additional 58 mg of zinc chloride was added.[15] After a total reaction time of 48 h, the reaction mixture at 20 °C was treated with 7 mL of tetrahydrofuran, 0.7 mL of acetic acid, and 0.3 mL of concentrated hydrochloric acid and then stirred for 30 min. The product was then isolated with methylene chloride in the usual manner and purified by dry silica gel chromatography with 20% ether in hexane to yield 2.17 g (90%) of hydroxy azide **5a**: mp 52.5–53.5 °C; $[\alpha]^{25}_D$ + 105° (*c* 2.3, chloroform); IR (neat) 3450, 3050, 3020, 2950, 2100, 1735, 1435, 1255, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (br d, J = 6.6 Hz, 1 H), 3.82 (s, 3 H), 4.23–4.51 (m, 1 H), 4.85 (d, J = 2.7 Hz, 1 H), 7.41 (br s, 5 H); mass spectrum, m/e 179 ($M^+ - N_3$). Anal. Calcd for $C_{10}H_{11}O_3N_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.48; H, 4.85; N, 18.77.

(2*R*,3*S*)-(+)-Methyl 3-Azido-2-benzoyl-3-phenylpropionate (5b). To a solution of 2.16 g (9.76 mmol) of the above hydroxy azide **5a** and 1.63 mL (1.18 g, 11.69 mmol) of triethylamine in 20 mL of methylene chloride was added 1.25 mL (1.51 g, 10.77 mmol) of benzoyl chloride and a few crystals of 4-(dimethylamino)pyridine. After being stirred for 1 h, the reaction mixture was processed with methylene chloride in the usual way and the resulting residue was purified by dry silica gel chromatography with 10% ethyl acetate in hexane to yield 3.00 g (94%) of azido benzoate **5b**: $[\alpha]^{26}_D$ +106° (*c* 2.6, chloroform); IR (neat) 3055, 3020, 2850, 2100, 1740, 1600, 1580, 1250, 1115, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 5.16 (d, J = 4.7 Hz, 1 H), 5.50 (d, J = 4.7 Hz, 1 H), 7.17–7.65 (m, 8 H), 7.98–8.21 (m, 2 H); mass spectrum, m/e 283 ($M^+ - N_3$). Anal. Calcd for $C_{17}H_{15}O_4N_3$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.78; H, 4.61; N, 13.00.

(2*R*,3*S*)-(−)-*N*-Benzoyl-3-phenylisoserine Methyl Ester (2). A mixture of 3.00 g (9.22 mmol) of the above azido benzoate **5b** and 600 mg of 10% palladium on carbon in 185 mL of methanol was vigorously stirred under hydrogen. After 15 h, the hydrogen was replaced with argon, the mixture was filtered, and the filtrate was allowed to stand at room temperature for 72 h. The methanol was then removed under reduced pressure to leave a crude solid, which was purified by precipitation from methylene chloride with cyclohexane (2.46 g, 89%). Crystallization of this material from chloroform then yielded 1.65 g (60%) of optically pure **2**: mp 184–185 °C (lit.[2a,b] mp 183–185 °C, 184–185 °C); $[\alpha]^{26}_D$ −48° (*c* 0.92, methanol) [lit.[2a] $[\alpha]^{23}_D$ −49.6° (methanol)]; IR (neat) 3350, 3060, 3025, 2950, 1740, 1640, 1600, 1580, 1520, 1485, 1450, 1440, 1290, 1260, 1220, 1115, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (br s, 1 H), 3.84 (s, 3 H), 4.63 (d, J = 2 Hz, 1 H), 5.74 (dd, J = 2 Hz, 9 Hz, 1 H), 6.98 (d, J = 9 Hz, 1 H), 7.18–7.59 (m, 8 H), 7.66–7.92 (m, 2 H); mass spectrum, m/e 300 (M^+ + 1), 281 ($M^+ - H_2O$).[2a,b] Anal. Calcd for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.48; H, 6.02; N, 4.80.

Samples of optically active **2** and racemic **2** were individually converted to the Mosher esters (see above).[10a] The ^1H NMR spectrum ($CDCl_3$) of the Mosher ester from racemic **2** displayed two sets of OCH_3 signals separated by 0.18 ppm; the corresponding ester from optically active **2** showed *only* the upfield signals under the same conditions.

(2*R*,3*S*)-*N*-Benzoyl-*O*-(methoxymethyl)-3-phenylisoserine Methyl Ester (6a, R′ = CH_3) and Free Acid (6a, R′ = H). A mixture of 135 mg (0.45 mmol) of alcohol **2**, 0.78 mL (579 mg, 4.5 mmol) of ethyldiisopropylamine, and 0.31 mL (326 mg, 4.0 mmol) of chloromethyl methyl ether (cancer suspect agent!) in

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4.5 mL of methylene chloride was stirred for 18 h at which time an additional 0.78 mL of ethyldiisopropylamine and 0.31 mL of chloromethyl methyl ether were added.[19a] After a total reaction time of 40 h, the reaction mixture was treated with aqueous sodium bicarbonate and then stirred for 30 min. The reaction product was isolated with methylene chloride in the normal manner and purified by dry silica gel chromatography with 10% ether in methylene chloride to give 127 mg (82%) of derivative **6a (R′ = CH_3)**: mp 126.5–127 °C; $[\alpha]^{26}_D$ −3.4° (*c* 1, chloroform); IR (neat) 3325, 3050, 3025, 2990, 2950, 2880, 2835, 2815, 1740, 1630, 1530, 1270, 1160, 1105, 1040, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.91 (s, 3 H), 3.76 (s, 3 H), 4.43–4.72 (m, 3 H), 5.75 (dd, *J* = 2 Hz, 9 Hz, 1 H), 7.00–7.60 (m, 9 H), 7.70–7.96 (m, 2 H); mass spectrum, *m/e* 344 (M^+ + 1). Anal. Calcd for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.15; H, 6.49; N, 4.12.

Hydrolysis of 127 mg (0.37 mmol) of **6a (R′ = CH_3)** was effected by treatment with 127 mg (0.92 mmol) of potassium carbonate in 4 mL of methanol and 2 mL of water for 15 h to give 122 mg (100%) of the corresponding acid **6a (R′ = H)**: mp 65–67 °C; $[\alpha]^{26}_D$ + 12° (*c* 1.1, chloroform); IR (neat) 3500–2300, 3440, 3300, 3060, 3040, 2950, 2900, 1740, 1650, 1600, 1580, 1525, 1158, 1120, 1055, 1030, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.86 (s, 3 H), 4.39–4.70 (m, 3 H), 5.82 (dd, *J* = 2 Hz, 9 Hz, 1 H), 7.25–7.55 (m, 9 H), 7.70–7.90 (m, 2 H), 9.25 (br s, 1 H); mass spectrum, *m/e* 330 (M^+ + 1).

(2*R*,3*S*)-*N*-Benzoyl-*O*-[(benzyloxy)methyl]-3-phenylisoserine Methyl Ester (6b, R′ = CH_3) and Free Acid (6b, R′ = H). The acetal was prepared (75% yield) with benzyl chloromethyl ether[19b] in a manner completely analogous with that described above for the methoxymethyl acetal. **6b (R′ = CH_3)**: mp 126–127 °C; $[\alpha]^{26}_D$ +6° (*c* 1.8, chloroform); IR (neat) 3325, 3050, 3020, 2940, 2875, 1740, 1630, 1520, 1270, 1110, 1040, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3 H), 4.06 (AB q, *J* = 12 Hz, δ_a–δ_b = 9 Hz, 2 H), 4.49–4.85 (m, 3 H), 5.78 (dd, *J* = 2 Hz, 9 Hz, 1 H), 6.86–7.56 (m, 14 H), 7.67–7.95 (m, 2 H); mass spectrum, *m/e* 419 (M^+). Anal. Calcd for $C_{25}H_{25}O_5N$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.35; H, 6.08; N, 3.27.

Hydrolysis of this ester as above furnished in 82% yield the corresponding acid **6b (R′ = H)**: mp 52.5–54 °C; $[\alpha]^{26}_D$ +21° (*c* 1.3, chloroform); IR (neat) 3800–2200, 3425, 3300, 1740, 1640, 1600, 1570, 1520, 1480, 1160, 1050, 1020, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (AB q, *J* = 12 Hz, δ_a–δ_b = 7 Hz, 2 H), 4.55–4.94 (m, 3 H), 5.28 (br s, 1 H), 5.86 (dd, *J* = 1 Hz, 9 Hz, 1 H), 6.89–7.54 (m, 14 H), 7.65–7.95 (m, 2 H), 9.69 (br s, 1 H); mass spectrum, *m/e* 406 (M^+ + 1).

(2*R*,3*S*)-*N*-Benzoyl-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-3-phenylisoserine Methyl Ester (6c, R′ = CH_3) and Free Acid (6c, R′ = H). This acetal was prepared (96% yield) with chloromethyl 2-(trimethylsilyl)ethyl ether[19c] in a manner completely analogous with that described above for the methoxymethyl acetal. **6c (R′ = CH_3)**: mp 67.5–68 °C; $[\alpha]^{26}_D$ +11° (*c* 1.2, chloroform); IR (neat) 3430, 3300, 3050, 3020, 2950, 2880, 1750, 1660, 1510, 1480, 1245, 1070, 1060, 1030, 1020, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.08 (s, 9 H), 0.56–0.77 (m, 2 H), 3.02–3.30 (m, 2 H), 3.76 (s, 3 H), 4.53–4.75 (m, 3 H), 5.73 (dd, *J* = 2 Hz, 9 Hz, 1 H), 7.14 (d, *J* = 9 Hz, 1 H), 7.20–7.58 (m, 8 H), 7.67–7.93 (m, 2 H); mass spectrum, 430 (M^+).

Anal. Calcd for $C_{23}H_{31}O_5NSi$: C, 64.30; H, 7.27; N, 3.26. Found: C, 64.16; H, 7.32; N, 3.29.

Hydrolysis of this ester as above furnished in 92% yield the corresponding acid **6c (R′ = H)**: mp 52–54 °C; $[\alpha]^{26}_D$ +20° (*c* 1.3, chloroform); IR (neat) 3700–2300, 3420, 3300, 3060, 3025, 2950, 2880, 1740, 1650, 1520, 1480, 1250, 1075, 1060, 1030, 1015, 860, 840, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.09 (s, 9 H), 0.55–0.77 (m, 2 H), 3.03–3.29 (m, 2 H), 4.46–4.83 (m, 3 H), 5.83 (dd, *J* = 2 Hz, 9 Hz, 1 H), 6.53 (br s, 1 H), 7.18–7.54 (m, 9 H), 7.68–7.96 (m, 2 H).

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine Ester with (−)-Isopinocampheol (7). To 100 mg (0.30 mmol) of acid **6a (R′ = H)**, 117 mg (0.76 mmol) of (−)-isopinocampheol (**8**), and 6.1 mg (0.05 mmol) of 4-(dimethylamino)pyridine in 0.28 mL of methylene chloride at 0 °C was added 82 mg (0.40 mmol) of *N*,*N*′-dicyclohexylcarbodiimide.[21] After being stirred for 5 min at 0 °C and 15 h at 20 °C, the reaction mixture was filtered with the aid of methylene chloride. Evaporation of the solvent and purification of the residue by dry silica gel chromatography with 5% ether in methylene chloride then furnished 99 mg (70%) of the protected isopinocampheyl ester: mp 85–89 °C; $[\alpha]^{26}_D$ +4° (*c* 0.7, chloroform); IR (neat) 3440, 3325, 3055, 3025, 2925, 1735, 1650, 1600, 1520, 1480, 1205, 1150, 1110, 1030, 915, 715, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 1.00 (d, *J* = 7 Hz, 3 H), 1.20 (s, 3 H), 1.6–2.80 (m, 7 H), 2.90 (s, 3 H), 4.59 (AB q, *J* = 7 Hz, δ_a–δ_b = 15.7 Hz, 2 H), 4.59 (d, *J* = 2.3 Hz, 1 H), 4.98–5.30 (m, 1 H), 5.78 (dd, *J* = 2.3 Hz, 8.6 Hz, 1 H), 7.10–7.60 (m, 9 H), 7.7–7.95 (m, 2 H).

The methoxymethyl protecting group was removed from a 61-mg (0.13 mmol) sample of the above compound through reaction at −20 °C with 83 μL (96 mg, 0.63 mmol) of bromotrimethylsilane in the presence of nine 4-Å molecular sieves in 0.90 mL of methylene chloride for 20 h.[19a] The product was isolated in the usual way and purified by dry silica gel chromatography with 5% ether in methylene chloride to give 51 mg (92%) of the isopinocampheyl ester **7**: mp 57–59 °C; $[\alpha]^{26}_D$ −15° (*c* 0.9, chloroform); IR (neat) 3350, 3060, 3020, 2920, 1730, 1645, 1600, 1580, 1520, 1480, 1450, 1270, 1218, 1115, 1030, 915, 800, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 1.00 (d, *J* = 7 Hz, 3 H), 1.20 (s, 3 H), 1.60–2.80 (m, 7 H), 3.34 (d, *J* = 4 Hz, 1 H), 4.61 (dd, *J* = 2 Hz, 4 Hz, 1 H), 5.05–5.38 (m, 1 H), 5.78 (dd, *J* = 2 Hz, 9 Hz, 1 H), 7.02 (d, *J* = 9 Hz, 1 H), 7.18–7.6 (m, 8 H), 7.7–7.95 (m, 2 H); mass spectrum *m/e* 422 (M^+). Anal. Calcd for $C_{26}H_{31}O_4N$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.16; H, 7.46; N, 3.20.

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine Ester with (−)-1,2;3,4-Di-*O*-isopropylidene-D-galactopyranose (7). To 103 mg (0.25 mmol) of acid **6b (R′ = H)**, 113 mg (0.43 mmol) of (−)-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose (**9**), and 3.1 mg (0.03 mmol) of 4-(dimethylamino)pyridine in 0.6 mL of methylene chloride was added 82 mg (0.38 mmol) of 2-dipyridyl carbonate.[20] The reaction mixture was stirred at 20 °C for 20 h, and then the product was isolated with methylene chloride in the usual way and purified by dry silica gel chromatography with 4% ether in methylene chloride to yield 151 mg (92%) of the protected ester: mp 60–63 °C; $[\alpha]^{26}_D$ −31° (*c* 0.8, chloroform); IR (neat) 3350, 3075, 3050, 3025, 2920, 2845, 1740, 1660, 1600, 1575, 1510, 1480, 1450, 1375, 1250, 1210, 1160, 1110, 1070, 1000, 915, 890, 800, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.33 (s, 3 H), 1.44 (s, 3 H), 1.52 (s, 3 H), 4.0–4.4 (m, 7 H), 4.50–4.90 (m, 4 H), 5.51 (d, *J* = 5 Hz, 1 H), 5.77 (dd, *J* = 2 Hz, 9 Hz, 1 H), 6.9–7.6 (m, 14 H), 7.95 (m, 2 H); mass spectrum, *m/e* 647 (M^+).

The (benzyloxy)methyl protecting group was removed from a 115-mg (0.18 mmol) sample of the above compound through treatment with 23 mg of 10% palladium on carbon in 2.3 mL of ethanol for 4 h at 60 °C under hydrogen.[19b] Isolation of the product in the normal manner and purification by dry silica gel chromatography with 5% ether in methylene chloride gave 88 mg (94%) of ester **7**: mp 189–190 °C; $[\alpha]^{26}_D$ −40° (*c* 0.9, chloroform); IR (Nujol) 3380, 3075, 3055, 3025, 1740, 1640, 1600, 1580, 1525, 1375, 1290, 1260, 1210, 1195, 1120, 1075, 1015, 720, 710, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 3 H), 1.32 (s, 3 H), 1.42 (s, 3 H), 1.56 (s, 3 H), 1.61 (br s, 1 H), 4.08–4.25 (m, 2 H), 4.26–4.45 (m, 3 H), 4.60 (m, 1 H), 4.71 (d, *J* = 2.1 Hz, 1 H), 5.52 (d, *J* = 5.0 Hz, 1 H), 5.74 (dd, *J* = 2.1 Hz, 9.2 Hz, 1 H), 7.03 (d, J = 9.2 Hz, 1 H), 7.05–7.76 (m, 8 H), 7.78 (d, *J* = 7.0 Hz, 2 H). Anal. Calcd for $C_{28}H_{33}O_9N$: C, 63.74; H, 6.31; N, 2.66. Found: C, 63.53; H, 6.32; N, 2.58.

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine Ester with Methyl Gibberellate (7). To 102 mg (0.25 mmol) of acid **6c (R′ = H)**, 108 mg (0.30 mmol) of methyl gibberellate (**10**, obtained by treatment of (+)-gibberellic acid with ethereal diazomethane), and 3.0 mg (0.03 mmol) of 4-(dimethylamino)pyridine in 1.0 mL of methylene chloride was added 70 mg (0.32 mmol) of 2-dipyridyl carbonate.[20] The mixture was stirred for 20 h at 20 °C, and then the product was isolated with methylene chloride in the usual manner and purified by preparative thin-layer chromatography with 10% ether in methylene chloride (three developments) to afford 114 mg (61%) of the protected ester: mp 105–107 °C; $[\alpha]^{26}_D$ +118° (*c* 1.3, chloroform); IR (neat) 3420, 3050, 3020, 2940, 2880, 1770, 1730, 1660, 1510, 1480, 1250, 1160, 1100, 1060, 1030, 860, 840, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.07 (s, 9 H), 0.55–0.78 (m, 2 H), 1.15 (s, 3 H), 1.47–2.38 (m, 11 H), 3.09 (AB q, *J* = 11 Hz, δ_a–δ_b = 53 Hz, 2 H), 3.05–3.40 (m, 2 H), 3.76 (s, 3 H), 4.61–4.71 (m, 3 H), 4.99 (br s, 1 H), 5.28 (br s, 1 H), 5.40 (d, *J* = 3.5 Hz, 1 H), 5.73–5.89 (m, 2 H), 6.31 (d, *J* = 9.4 Hz, 1 H), 7.05 (d, *J* = 9 Hz, 1 H), 7.18–7.58 (m, 8 H), 7.66–7.96 (m, 2 H).

The [2-(trimethylsilyl)ethoxy]methyl protecting group was removed from a 110-mg (0.15 mmol) sample of the above compound through contact for 4 h at 20 °C with 0.5 mL of acetonitrile containing 5% of 40% aqueous hydrofluoric acid.[19c] The product was isolated in the usual fashion and purified by preparative thin-layer chromatography with 20% ether in methylene chloride to give 64 mg (70%) of ester **7**: mp 127–130 °C; $[\alpha]^{26}_D$ +139° (*c* 1.2, chloroform); IR (neat) 3400, 3050, 3020, 2925, 1770, 1730, 1650, 1515, 1480, 1160, 1100, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.45–2.38 (m, 10 H), 3.10 (AB q, J = 11 Hz, δ_a–δ_b = 54 Hz, 2 H), 3.74 (s, 3 H), 4.71 (d, J = 2 Hz, 1 H), 4.99 (br s, 1 H), 5.29 (br s, 1 H), 5.42 (d, J = 3.5 Hz, 1 H), 5.79 (dd, J = 2.3 Hz, 9.4 Hz, 1 H), 5.84 (dd, J = 3.5, 9.4 Hz, 1 H), 6.30 (d, J = 9.4 Hz, 1 H), 6.98 (d, J = 9.4 Hz, 1 H), 7.25–7.61 (m, 8 H), 7.61–7.87 (m, 2 H); mass spectrum, *m/e* 628 (M^+ + 1), 627 (M^+). Anal. Calcd for $C_{36}H_{37}O_9N$: C, 68.88; H, 5.94; N, 2.23. Found: C, 68.68; H, 5.84; N, 2.07.

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Registry No. **1**, 33069-62-4; **2**, 32981-85-4; **3**, 4510-34-3; **4a**, 99528-63-9; **4b**, 99528-64-0; **4c**, 99528-65-1; **5a**, 99458-15-8; **5b**, 99458-16-9; **6a** (R′ = CH_3), 99458-17-0; **6a** (R′ = H), 99458-20-5; **6a** (**8** ester), 99458-23-8; **6b** (R′ = CH_3), 99458-18-1; **6b** (R′ = H), 99458-21-6; **6b** (**9** ester), 99458-24-9; **6c** (R′ = CH_3), 99458-19-2; **6c** (R′ = H), 99458-22-7; **6c** (**10** ester), 99475-54-4; **7** (**8** ester), 99458-25-0; **7** (**9** ester), 99458-26-1; **7** (**10** ester), 99458-27-2; **8**, 1196-00-5; **9**, 4064-06-6; **10**, 510-50-9; chloromethyl 2-(trimethylsilyl)ethyl ether, 76513-69-4; phenylacetylene, 536-74-3; 3-phenyl-2-propyn-1-ol, 1504-58-1; azidotrimethylsilane, 4648-54-8; chloromethyl methyl ether, 107-30-2; benzyl chloromethyl ether, 3587-60-8.

Stereoselective Syntheses of (±)-Daunosamine, (±)-Vancosamine, and (±)-Ristosamine from Acyclic Precursors

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Stereoselective syntheses of *N*-trichloroacetyl derivatives of (±)-daunosamine (**14**) and (±)-vancosamine (**25**) from simple acyclic precursors are described. Modification of the sequence used for preparation of daunosamine resulted in a novel stereospecific total synthesis of the *N*-trichloroacetyl derivative of (±)-ristosamine (**30**).

Daunosamine[1] (**1**), the sugar fragment in the therapeutically important anticancer antibiotics daunorubicin[2] and adriamycin,[3] is the best known and most often synthesized[4] of the naturally occurring 2,3,6-trideoxy-3-aminohexoses shown in Figure 1. Though less well-known, vancosamine[5] (**2**), ristosamine[6] (**3**), and acosamine[4f] (**4**) have also been of intense synthetic interest since it was found that replacement of daunosamine (**1**) in the parent antibiotics with ristosamine (**3**) or acosamine (**4**) produced analogues, which, though somewhat less active, are significantly less toxic.[7]

In conjunction with our continuing efforts to establish new methodology for the synthesis of 2,3,6-trideoxy-3-aminohexoses from simple acyclic precursors,[4e] a general route for the stereoselective preparation of racemic daunosamine (**1**) and vancosamine (**2**) was developed. A novel stereospecific preparation of racemic ristosamine (**3**) from an intermediate in the daunosamine sequence was also accomplished.

(±)-Daunosamine. The plan devised for the synthesis of the *N*-trichloroacetyl derivative of daunosamine (Scheme I) is based, in part, on our earlier work[4e] which established that cis-hydroxylation of acyclic allyl amide systems produces predominantly the *lyxo* stereochemistry that is present in daunosamine (**1**).

Overman reaction[8] of sorbyl alcohol (**5**) (catalytic NaH, Cl_3CCN, –20 °C; xylene, reflux) furnished the deconjugated diene **6a** in quantitative yield. Initial efforts to functionalize C-1 for subsequent conversion to an aldehyde were unsuccessful; hydroboration of either the amide **6a** or the amine **6b** with 9-BBN resulted in complex mixtures of products. Ultimately, the desired functionalization was obtained through free radical addition of benzenethiol to the terminal olefin[9] (AIBN, 80–90 °C, 30 h) which regiospecifically produced the sulfide **7a** in 87% yield.

An alternate preparation of **7a** was carried out to confirm the structure of **7a** and also to explore the conceptual potential for performing optically active aminohexose synthesis from chiral allyl alcohol precursors. Wittig reaction of **8** with 3-(phenylthio)propanal[10] (**9**) furnished the

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