hydrocarbon **4c** (0.31 g, 83%), which had the expected spectral properties: ^{1}H NMR δ ($CDCl_3$) 0.95 (t, 3 H, J = 124.5 Hz).

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Registry No. 1 (X = Cl), 935-56-8; **1** (X = $^{13}CH_2OH$), 65305-16-0; **1** (X = $^{13}CH_2OTs$), 87984-84-7; **1c**, 85553-56-6; **1d**, 50530-21-7; **2** (X = Cl), 2064-03-1; **2** (X = $^{13}CH_2OH$), 73948-81-9; **2** (X = $^{13}CH_2OTs$), 87969-53-7; **2c**, 80326-44-9; **2d**, 73948-77-3; **3** (X = Br), 13474-70-9; **3** (X = $^{13}CH_2OH$), 73948-82-0; **3c**, 76450-98-1; **3d**, 73948-78-4; **4c**, 80326-45-0; **5** (X = $^{13}CH_2OH$), 73948-83-1; **5** (X = Br), 77379-00-1; **5c**, 80326-46-1; **5d**, 73948-79-5; **6c**, 87969-51-5; **6d**, 87969-55-9; **7** (X = Br), 59346-69-9; **7c**, 87969-52-6; **8c**, 80326-47-2; **9**, 77378-99-5; **10**, 87969-54-8; **11**, 31991-53-4; **13**, 87969-56-0; **14** (R = H), 5164-64-7; **14** (R = CH_3), 20609-40-9; **16** (R = CH_3), 87969-60-6; **17** (R = CH_3), 10555-48-3; **21**, 87969-57-1; **23**, 87969-58-2; **25**, 87969-59-3; **27**, 87969-61-7; **28**, 87969-62-8; **29**, 87969-63-9; *p*-toluenesulfonylhydrazine, 1576-35-8; methyl iodide, 74-88-4.

Total Syntheses with Tricyclooctanone Building Blocks. Loganin Aglucon 6-Acetate[1]

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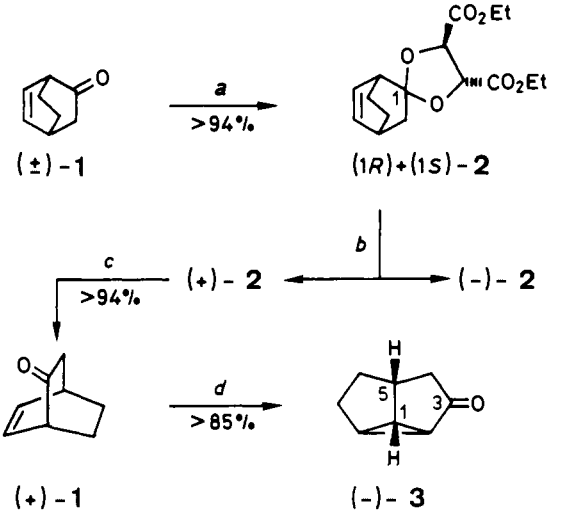
Abstract: A total synthesis of the monoterpene loganin aglucon 6-acetate in 17 steps from 1,3-cyclohexadiene is described. It involves the photochemical generation of enantiomerically pure tricyclo[3.3.0.0^{2,8}]octan-3-one as the key step and it employes an improved procedure for the resolution of bicyclo[2.2.2]octenone, the starting material for the triplet-sensitized rearrangement to the key building block. The synthesis is distinguished by a higher overall yield (ca. 7% in 17 steps from 1,3-cyclohexadiene) than previous efforts and is devoid of any separation problems, so that it can be carried through in multigram batches.

We have recently outlined the concept of a very versatile approach to the synthesis of polycyclopentanoid natural products with readily accessible optically active building blocks.[2] The concept involves the photochemical generation of *enantiomerically pure* tricyclo[3.3.0.0^{2,8}]octan-3-ones as the key step. The parent and most versatile of these structural units, **3**, is formed in >85% yield[3] in the acetone-sensitized oxadi-π-methane rearrangement of **1** (Scheme I).[4,5] Compound **3** is readily accessible in multigram batches from 1,3-cyclohexadiene, as a racemate, in four steps and ca. 54% overall yield and in optically active form in six steps and 19% overall yield for each enantiomer. Subsequent to our initial report[2a] the use of *racemic*, more highly substituted tricyclo-[3.3.0.0^{2,8}]octan-3-ones of less versatile synthetic potential has been described.[6]

We now report the synthesis of enantiomerically pure (enantiomeric excess >98%) loganin aglucon 6-acetate (**11**)[7] from

Scheme I[3]



[a] Diethyl (*R,R*)-tartrate, *p*-TsOH, toluene, reflux. [b] Chromatography, see Experimental Section. [c] 1 N HCl, THF, 40 °C. [d] 1% acetone solution, $h\nu$ (λ = 300 nm); see ref 4.

(1*S*,5*R*)-(−)-**3** (Scheme II), which also includes an improved procedure for the resolution of (±)-**1** into its enantiomers. The iridoid loganin[7] is a key biosynthetic intermediate for indole and monoterpene alkaloids and other natural products.[8] In earlier

(1) The analogous synthesis of *d,l*-loganin aglucon 6-acetate was presented at the Synthesis in Organic Chemistry Conference, Oxford, 1981.

(2) (a) Demuth, M.; Raghavan, P. R.; Schaffner, K. *Abstr. ESOC I Conf.* **1979**, 312. (b) Demuth, M.; Chandrasekhar, S.; Nakano, K.; Raghavan, P. R.; Schaffner, K. *Helv. Chim. Acta* **1980**, *63*, 2440. (c) Carter, C.; Chandrasekhar, S.; Demuth, M.; Nakano, K.; Schaffner, K. *Abstr. VIII IUPAC Symp. Photochem.* **1980**, 100. (d) Schaffner, K.; Demuth, M. *Chimia* **1981**, *35*, 437. (e) Demuth, M.; Schaffner, K. *Angew. Chem.* **1982**, *94*, 809; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820.

(3) All yields refer to isolated pure products.

(4) Demuth, M.; Raghavan, P. R.; Carter, C.; Nakano, K.; Schaffner, K. *Helv. Chim. Acta* **1980**, *63*, 2434.

(5) The photochemical formation of **3** was first reported by Givens et al. (Givens, R. S.; Oettle, W. F.; Coffin, R. L.; Carlson, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 3957) subsequent to the synthetically unpractical diazo ketone route of Monti et al. (Monti, S. A.; Bucheck, D. J.; Shepard, J. S. *J. Org. Chem.* **1969**, *34*, 3080).

(6) Stevens, K. E.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1980**, 990. Callant, P.; De Wilde, H.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2079. Callant, P.; Ongena, R.; Vandewalle, M. *Ibid.* **1981**, *37*, 2085. Yates, P.; Stevens, K. E. *Ibid.* **1981**, *37*, 4401.

(7) Structural elucidation: (a) Brechbühler-Bader, S.; Coscia, C. J.; Loew, P.; v. Szczepanski, C.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1968**, 136. (b) Lentz, Jr., P. J.; Rossmann, M. G. *Ibid.* **1969**, 1269. (c) Inouye, H.; Yoshida, T.; Tobita, S. *Tetrahedron Lett.* **1968**, 2945. (d) Battersby, A. R.; Hall, E. S.; Southgate, R. *J. Chem. Soc. C* **1969**, 721.

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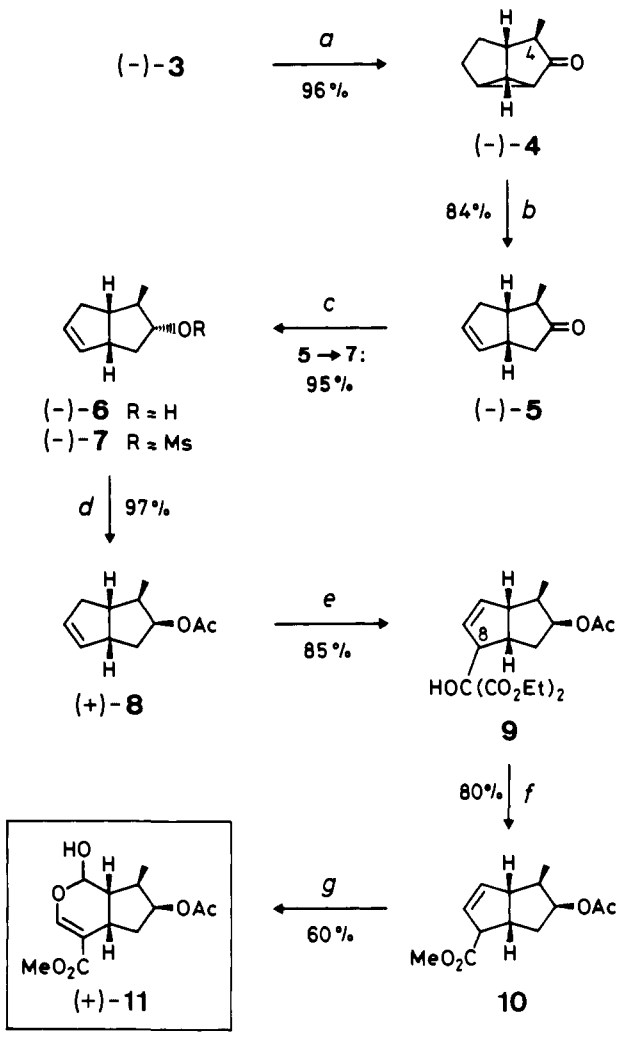
Scheme II[a]



[a] NaH, MeI, THF, 50 °C. [b] Nafion-TMS, toluene, 80 °C. [c] $NaBH_4$, MeOH, 0 °C; $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C. [d] Et_4NOAc, acetone, reflux. [e] $OC(CO_2Et)_2$, $TiCl_4$, CH_2Cl_2, room temperature, 16 h. [f] 10% KOH, room temperature, 18 h; $NaIO_4$, pyridine (cat.), room temperature, 12 h; CH_2N_2, ether–MeOH, 0 °C to room temperature; Ac_2O, pyridine, 5 °C. [g] OsO_4(cat.), *N*-methylmorpholine *N*-oxide, *t*-BuOH, THF, H_2O, room temperature; $NaIO_4$, dioxane, H_2O, 0 °C.

work, syntheses of *d,l*-loganin[9] and, in particular, a very short enantioselective synthesis of the natural enantiomer of loganin[10] have been described. Our own synthesis[11] is distinguished from these previous efforts by a higher overall yield of **11** and by the fact that the entire sequence met with no separation problems. Scaling-up of this synthesis to larger than mere milligram quantities should therefore be feasible.

Results and Discussion

The resolution of (±)-**1** was carried out via the mixture of diastereoisomeric acetals **2** which was formed quantitatively from (±)-**1** and diethyl (*R,R*)-(+)-tartrate (Scheme I) and which could be smoothly separated by chromatography on a multigram scale. The use of tartrate considerably improved the resolution procedure over the former method[4] employing 1,4-dimethoxybutane-2,3-diol, notably with respect to the acetalization (quantitative conversion to **2**) and the ease of chromatographic separation (32% yield of each diastereomeric acetal). The acid-catalyzed hydrolysis of (+)-**2** gave (+)-**1** almost quantitatively in >98% enantiomeric excess. The enone (+)-**1** was then photorearranged to (-)-**3** as described previously.[4,12] The highly stereoselective methylation to (-)-**4**[13] and its isomerization, catalyzed with Nafion-Me_3Si (a perfluorated trimethylsilyl sulfonate resin), to (-)-**5** have already been described for the racemates.[2b,14,15] Prolonged treatment with Nafion-TMS led to some endo epimerization of the methyl group of **5**, but this could be avoided by careful monitoring of the reaction using gas chromatography.

The reduction of (-)-**5** with $NaBH_4$ gave exclusively the endo alcohol (-)-**6**. For the transformation of this product into **11** a strategy was adopted which had already been employed in the syntheses of *d,l*-loganin.[16] The endo alcohol (-)-**6** was converted to the mesylate (-)-**7** and epimerized to the exo acetate (+)-**8** by treatment of the latter with tetraethylammonium acetate. The subsequent ene synthesis with diethyl oxomalonate when catalyzed with $TiCl_4$ in the temperature range from 0 to 20 °C afforded better yields of **9** than when BF_3 or $SnCl_4$ was used as in the literature procedure.[17] The product **9** was sterically nonuniform at C-8; this, however, is irrelevant with regard to the target structure. The degradation to the ca. 1:1 mixture of epimeric methyl esters **10** was achieved in high yield in four steps: alkaline hydrolysis and decarboxylation, cleavage of the α-hydroxy acid with periodate, esterification of the acid, and reacetylation of the hydroxyl group. In the next step, the double bond of the epimeric mixture **10** was hydroxylated by either of two known procedures, treatment with a stoichiometric amount of OsO_4[9c] or with a catalytic amount in combination with *N*-methylmorpholine *N*-oxide.[18] The yield of the final product was somewhat higher under the latter conditions. Finally, cleavage with $NaIO_4$[9c] gave loganin aglucon 6-acetate (**11**). The IR and ^1H NMR spectra of the product were fully compatible with those reported for synthetic (±)-**11**,[9c] and the specific optical rotation, $[\alpha]_D$ +2°, was in accord with the literature value.[10]

Experimental Section

General. Melting points were taken under a microscope on a Kofler hot plate and are uncorrected. Specific optical rotations, $[\alpha]_D$, were measured at 23 °C in $CHCl_3$, *c* in parentheses, experimental error ±5%. ^1H NMR spectra were measured in $CDCl_3$, unless stated otherwise, on Bruker WP-80 (80 MHz) and WH-270 (270 MHz) instruments in FT mode. The chemical shifts are in δ units (with $(CH_3)_4Si$ as internal reference) and the coupling constants (*J*) in Hz; abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). IR spectra were run in $CHCl_3$, unless stated otherwise, on Perkin-Elmer 137 and 700 instruments and are given in cm^{-1}. Mass spectra (MS; in *m/e*) were recorded on a Varian MAT CH5 instrument at 70 eV. GLC analyses were performed with a Varian Aerograph 1700 instrument equipped with

(8) Battersby, A. R. "The Alkaloids" In "Specialist Periodical Reports"; Saxton, J. E., Ed.; The Chemical Society: London, 1971; Vol. 1, p 31.
(9) (a) Büchi, G.; Carlson, J. A.; Powell, Jr., J. E.; Tietze, L.-F. *J. Am. Chem. Soc.* **1973**, *95*, 540. (b) Hiroi, K.; Miura, H.; Kotsuji, K.; Sato, S. *Chem. Lett.* **1981**, 559. (c) Fleming, I.; Au-Yeung, B.-W. *Tetrahedron* **1981**, *37*, Suppl. 1, 13. (d) See also ref 13.
(10) Partridge, J. J.; Chadha, N. K.; Uskokovič, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532.
(11) Our synthesis formally constitutes also a total synthesis of loganin, since the aglucon acetate (+)-**11** has already been transformed into the natural compound[7d] via the glucoside pentaacetate.[9a,10]
(12) The 1*S*,5*R* chirality has been assigned to (-)-**3** on the basis of its CD Cotton effect.[4] The transformation to the natural enantiomer of loganin now confirms the validity of the octant rule for bicyclo[3.1.0]hexan-2-ones (Schaffner, K.; Snatzke, G. *Helv. Chim. Acta* **1965**, *48*, 347. Djerassi, C.; Klyne, W.; Norin, T.; Ohloff, G; Klein, E. *Tetrahedron* **1965**, *21*, 163. Lightner, D. A.; Jackman, D. E. *Tetrahedron Lett.* **1975**, 3051) when applied to bridged derivatives such as **3**.
(13) A sterically unselective synthesis of (±)-**4** has recently been described: Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399. Subsequent to our communication,[2e] this material has also been used for a synthesis of racemic loganin (Kon, K.; Isoe, S. *Helv. Chim. Acta* **1983**, *66*, 755).
(14) Demuth, M.; Mikhail, G. *Tetrahedron* **1983**, *39*, 991.
(15) Demuth, M.; Mikhail, G.; George, M. V. *Helv. Chim. Acta* **1981**, *64*, 2759.
(16) The endo → exo epimerization of the hydroxy group by way of an S_N2 substitution of the mesylate[9a] and an ene-synthetic step[9c] have been described for similar intermediates.
(17) Salomon, M. F.; Pardo, S. N.; Salomon, R. G., *J. Am. Chem. Soc.* **1980**, *102*, 2473. Pardo, S. N.; Ghosh, S.; Salomon, R. G. *Tetrahedron Lett.* **1981**, *22*, 1885 and references therein.
(18) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

a flame ionization detector coupled to a Spectra Physics Autolab System I computing integrator. OV 101 glass capillary columns of 20- and 35-m length were used, with nitrogen as the carrier gas. The solvents were purified by using standard procedures. All reactions were run under argon atmosphere. The homogeneity of the products was ≥98% by GLC and ^{1}H NMR, unless stated otherwise. The elemental analyses were determined by Dornis and Kolbe, Mülheim a.d. Ruhr.

Diethyl Tartrate Acetals (1*R*)- and (1*S*)-2. A solution of (±)-1[2e,19] (10 g, 82 mmol), *p*-toluenesulfonic acid (0.35 g, 1.84 mmol), and diethyl (*R*,*R*)-(+)-tartrate (35 g, 170 mmol; $[\alpha]_D$ +7.9°, neat) in 20 mL of benzene was refluxed in a Dean–Stark apparatus. After 50 h the reaction mixture was cooled to room temperature and washed with five 100-mL portions of H_2O. The organic layer was separated and dried, and the solvent was evaporated. The residue was 25.89 g (96%) of a 1:1 mixture of the diasteroisomeric acetals **2** (94% purity by GLC; ca. 3% of the remainder was diethyl (+)-tartrate). The material was passed in 5-g portions through two Merck ready-made columns (Li-Chroprep SI 60, type C, mesh 63–125; solvent toluene–1% ether; pressure 24 bar) connected in series. A typical separation was as follows: fractions 1 and 5 contained each 0.75 g of (−)-**2** and (+)-**2**, respectively, with purities of ≥99%. Fractions 2 and 4 (each ca. 1.45 g) were strongly enriched with (−)-**2** and (+)-**2**, respectively, and fraction 3 (ca. 0.5 g) was 1:1 mixed. The enriched fractions were passed once more through the same columns using the same solvent mixture, affording another ~0.85 g of each isomer in pure form. The yields from 5 g of crude **2** were thus ca. 1.6 g of each diastereoisomer (separation 64% of the total).

Data for (+)-**2**: $[a]_D$ +65° (0.5); NMR 1.13 + 1.17 (2 t, each 3 H and J = 7), ca. 1.2–2.1 (6 H, m), ca. 2.5 (2 H, m), 4.11 + 4.15 (2 q, each 2 H and J = 7), 4.59 + 4.66 (2 d, each 1 H and J = 4.5), ca. 6.1 + 6.2 (2 m, each 1 H); IR (CCl_4) 1770, 1755, 1610, 1380, 1215, 1135, 1035; MS 310 (M^+, $C_{16}H_{22}O_6$), 231 (base peak),115, 80, 43, 29.

(−)-**2**: $[\alpha]_D$ −68.6° (2.31); NMR 1.12 + 1.16 (2 t, each 3 H and J = 7), ca. 1.2–2.1 (6 H, m), ca. 2.5 (2 H, m), 4.11 + 4.15 (2 q, each 2 H and J = 7), 4.63 + 4.67 (2 d, each 1 H and J = 4.5), ca. 6.1 + 6.2 (2 m, each 1 H); IR and MS data identical with those for (+)-**2**.

(1*R*,4*R*)-(+)- and (1*S*,4*S*)-(−)-Bicyclo[2.2.2]oct-5-en-2-ones (1). A solution of (+)-**2** (1.33 g, 4.29 mmol) in 50 mL of EtOH and 20 mL of 10% aqueous HCl was heated to 50 °C for 48 h. After cooling to room temperature 100 mL of H_2O was added and the mixture was extracted with three 30-mL portions of hexane. The combined organic layers were washed with aqueous $NaHCO_3$ solution. Evaporation of the solvent gave 492 mg (94%) of (+)-**1** ($[\alpha]_D$ + 512° (0.55)) as a colorless semicrystalline material. Hydrolysis of (−)-**2** gave (−)-**1** ($[\alpha]_D$ −520° (0.26)); both preparations exhibited enantiomeric purities of > 98% (see ref 4 for the analytical data of (+)- and (−)-**1**).

(1*S*,5*R*)-(−)-Tricyclo[3.3.0.0^{2,8}]octan-3-one (3). See ref 4 for the experimental details of the photochemical rearrangement of (+)-**1** and the analytical data of the product (−)-**3** ($[\alpha]_D$ −56° (0.38)).

(−)-4-*exo*-Methyltricyclo[3.3.0.0^{2,8}]octan-3-one (4). NaH (0.48 g, 50% oil suspension, 10 mmol) was washed with pentane and then suspended in 5 mL of freshly distilled THF. A solution of (−)-**3** (1.15 g, 9.4 mmol) in THF was added dropwise under stirring at room temperature. After the mixture had been refluxed for 1 h and cooled again to room temperature, 2 mL of methyl iodide in 5 mL of THF was poured into it. The temperature was raised to 50 °C and the methylation was monitored by GLC. It was important not to warm above 55 °C in order to minimize dimethylation. The reaction was completed within 4 h. Excess NaH was destroyed by the addition of 0.5 mL of MeOH. The solvents were then removed in vacuo, and the residue was extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 1.256 g of (−)-**4** (97% purity by GLC; 96% yield). The product contained 2–3% of the dimethyl homologue which was readily removed in subsequent purification steps. For analytical purposes a sample of (−)-**4** was distilled at 60–65 °C (0.7 torr): $[\alpha]_D$ −62° (0.9); NMR, see ref 14 for the data of (±)-**4**; IR 1720, 1450, 1185, 940, 875, 830; MS 136 (M^+, $C_9H_{12}O$), 121, 108, 93, 80 (base peak), 53, 39.

(−)-4-*exo*-Methylbicyclo[3.3.0]oct-7-en-3-one (5). The experimental details for the Nafion-TMS induced rearrangement of **4** to **5** have already been described for racemic material,[14] including the analytical data of the product (±)-**5**[15] (for a detailed NMR analysis see ref 14). (−)-**5**: $[\alpha]_D$ −38.5° (0.93).

(19) Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211. We have improved the overall yield of **1** to 64% by running the Diels–Alder reaction with very pure 1,3-cyclohexadiene (Fluka) and in the presence of 2% hydroquinone. In addition, the chloronitrile adduct was hydrolyzed by adding the KOH solution at 0 °C and warming the mixture slowly to room temperature, instead of adding KOH at higher temperature as described.

(−)-4-*exo*-Methylbicyclo[3.3.0]oct-7-en-3-*endo*-ol (6). $NaBH_4$ (0.57 g, 15 mmol) was added in portions to a stirred solution of (−)-**5** (1.18 g, 8.7 mmol) in MeOH (10 mL) at 0 °C. The reaction was quenched after 1.5 h by the addition of acetone (2 mL) and stirring was continued for another 15 min. The solvents were then removed in vacuo and the residue dissolved in ether–H_2O. After three extractions with ether, the combined organic portions were shaken with brine and finally dried over $MgSO_4$. Evaporation of the solvent afforded 1.185 g of (−)-**6** (98% purity by GLC; 97% yield). For analytical purposes a sample of the colorless oily (−)-**6** was distilled at 58 °C (0.7 torr): $[\alpha]_D$ −13.3° (0.39); NMR 0.99 (3 H, d, J = 7), ca. 1.1–1.4 (2 H, m), ca. 1.6 (1 H, m, exchangeable with D_2O), ca. 2.1 + 2.2 + 2.3 + 2.6 + 3.0 + 5.6 + 5.7 (7 m, each 1 H), 3.62 (1 H, q, J = 8); IR (film) 3390, 1615, 1090; MS 138 (M^+, $C_9H_{14}O$), 120, 105 (base peak), 79. Anal. Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 78.32; H, 10.06.

(−)-4-*exo*-Methylbicyclo[3.3.0]oct-7-en-3-*endo*-yl Mesylate (7). (−)-**6** (0.76 g, 5.4 mmol) was dissolved in dichloromethane (15 mL). To the stirred solution at 0 °C were then added triethylamine (0.75 g, 7.4 mmol) and methanesulfonyl chloride (0.75 g, 6.6 mmol). After 1-h reaction time, the mixture was poured into chilled H_2O. The organic layer was then separated and consecutively washed with ice-cold 10% HCl and $NaHCO_3$ solutions. After drying of the organic portion over $MgSO_4$, the solvent was removed in vacuo and (−)-**8** was obtained as a colorless oil (1.19 g). (−)-**7** (not purified; >96% by GLC): $[\alpha]_D$ − 27° (0.62); NMR 1.08 (3 H, d, J = 8), ca. 1.6 + 1.7 + 3.1 + 5.6 + 5.7 (5 m, each 1 H), ca. 2.0–2.3 + 2.4–2.7 (2 m, each 2 H), 2.99 (3 H, s), 4.46 (1 H, q, J = 8); IR (film) 1620, 1340, 1165, 940, 865; MS 216 (M^+, $C_{10}H_{16}O_3S$), 134, 120, 105 (base peak), 79, 55, 41.

(+)-4-*exo*-Methylbicyclo[3.3.0]oct-7-en-3-*exo*-yl Acetate (8). (−)-**7** (0.75 g, 3.5 mmol) was dissolved in acetone (10 mL) and refluxed for 12 h after the addition of anhydrous (dried at 60 °C (10^{-2} torr) for 2 h) tetraethylammonium acetate (1 g, 5.3 mmol). For the workup, the solvent was evaporated and the residue taken up in dichloromethane and H_2O. After repeated careful washing with H_2O, the organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent afforded a light yellow oily residue (0.742 g), which was purified by Kugelrohr distillation [70 °C (1 torr)], yielding pure (+)-**8** as a colorless oil (0.725 g, 97% yield). (+)-**8**: $[\alpha]_D$ +31.5° (0.46); NMR 0.98 (3 H, d, J = 7), ca. 1.7 + ca. 2.0–2.2 (2 m, each 2 H), 3.3 + 5.1 + 5.5 + 5.6 (4 m, each 1 H), 2.04 (3 H, s), 2.40 (1 H, q, J = 8), 2.55 (1 H, dd, J = 8, 18, with fine structure); IR (film) 1725, 1625, 1240, 1185, 1020; MS 138, 120 [M^+($C_{11}H_{16}O_2$) − AcOH], 105, 79, 59, 43 (base peak). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.15; H, 8.82.

Mixture of Diethyl 3-*exo*-Acetoxy-4-*exo*-methylbicyclo[3.3.0]oct-6-en-8-yl, Hydroxymalonates (8-*endo*- and 8-*exo*-9). (+)-**8** (0.35 g, 1.9 mmol) and freshly distilled diethyl oxomalonate (0.87 g, 5 mmol) were dissolved in 10 mL of dichloromethane and cooled to 0 °C. $TiCl_4$ (0.5 mL, 4.5 mmol) was then added in one portion to the stirred reaction mixture. The ice bath was removed and the reaction continued at ambient temperature during 16 h. The color of the mixture changed from initially light yellow to brown. The reaction was worked up by addition of cold H_2O followed by repeated extraction with dichloromethane. After the organic layer has been separated and dried over $MgSO_4$, the solvent was removed in vacuo and a brownish residue was obtained. This material was directly transferred to a Kugelrohr and excess diethyl oxomalonate was distilled off at 40–60 °C (10^{-2} torr). The residue (0.584 g, 85% yield) showed on GLC a ca. 1:1 mixture of the diastereoisomers **9**, which was used without further purification for the subsequent steps in the synthesis. For analytical purposes, a sample from a batch of (±) material was subjected to column chromatography (Florisil, 25-fold, 60–100 mesh). The two isomers were eluted with toluene–5% dichloromethane and with toluene–20% dichloromethane in the following order: (a) 8-*endo*-**9**, NMR 0.96 (d, J = 7, 3 H), 1.30 + 1.33 (2 t, J = 6, each 3 H), ca. 1.6–3.0 (m, 6 H), 2.01 (s, 3 H), 3.95 (s, 1 H, exchangeable with D_2O), 4.28 + 4.30 (2 q, J = 6, each 2 H), ca. 5.1–5.4 (m, 3 H); IR (film) 3490, 1740, 1620, 1450, 1370, 1240, 1020; MS 294 [M^+($C_{18}H_{26}O_7$) − AcOH], 257, 239, 221, 176, 147, 119 (base peak), 43. Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.02; H, 7.34. Found: C, 60.78; H, 7.60. (b) 8-*exo*-**9**, NMR 1.0 (d, J = 7, 3 H), 1.30 + 1.33 (2 t, J = 6, each 3 H), ca. 1.6–3.4 (m, 7 H, including 1 H exchangeable with D_2O), 2.03 (s, 3 H), 4.28 + 4.30 (2 q, J = 6, each 2 H), ca. 5.2 + 5.4 + 5.9 (3 m, each 1 H); IR and MS essentially idential with those of the 8-endo isomer of **9**.

Mixture of 8-Endo and 8-Exo Epimers of Methyl 3-*exo*-Acetoxy-4-*exo*-methylbicyclo[3.3.0]oct-6-en-8-anecarboxylates (10). The 1:1 mixture of 8-epimers of **9** (0.3 g, 0.82 mmol) was degraded, without intermediate purification, following a known procedure for analogous cases:[17] hydrolysis with KOH, bis-decarboxylation with $NaIO_4$ in the presence of a catalytic amount of pyridine, and esterification with CH_2N_2 in a 1:1 ether–methanol solution (0.5 h at 0 °C, then warming up to room temperature), followed by the addition of formic acid to destroy excess

CH_2N_2, washing with H_2O, and drying (Na_2SO_4) of the organic solvents prior to evaporation. The crude product was acetylated in 1:1 acetic anhydride-pyridine (5 °C, 8 h). Evaporation at 10^4 torr afforded **10** as a ca. 1:1 mixture of epimers (by GLC) which was distilled in the Kugelrohr at 80–90 °C (10^1 torr) to give 145 mg of **10** (80% yield).

The ca. 1:1 composition of the mixture **10** was determined by NMR, by using, as a reference, the spectra of the known[9c] 8-*exo*-**10** and of the *endo*-carbomethoxy epimer, which was obtained by chromatographic separation of the epimeric mixture **9** and by separate degradation of 8-*endo*-**9**.

8-*endo*-**10**: NMR (CCl_4) 0.95 (3 H, d, J = 7), ca. 1.4–3.0 (5 H, m), 1.98 + 3.70 (2 s, each 3 H), ca. 3.2 + ca. 5.1 (2 m, each 1 H), ca. 5.3 (m, 2 H); IR (film) 1740, 1625, 1435, 1370, 1240, 900; MS 154 [M^+($C_{13}H_{18}O_4$)–AcOH], 139, 119 (base peak), 95, 59, 43. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56. Found: C, 65.81; H, 7.63.

Loganin Aglucon 6-Acetate (11). The highest yield was achieved when the hydroxylation of the epimeric mixture **10** (110 mg, 0.51 mmol) was carried out with a catalytic amount of OsO_4 in combination with *N*-methylmorpholine *N*-oxide in *tert*-butyl alcohol–tetrahydrofuran–H_2O at room temperature.[18] Cleavage of the crude product with $NaIO_4$ in aqueous dioxane at 0 °C[9c] gave 66 mg **11** (60% yield), $[\alpha]_D$ +2° (0.5).[10] The ^1H NMR and IR spectra were in agreement with the data given[9c] for (±)-**11**.

Registry No. (±)-**1**, 68908-13-4; (+)-**1**, 16196-15-9; (+)-**2**, 88195-48-6; (–)-**2**, 88106-35-8; (–)-**3**, 77551-15-6; (–)-**4**, 88195-49-7; (–)-**5**, 88195-50-0; (–)-**6**, 88106-36-9; (–)-**7**, 88106-37-0; (+)-**8**, 88106-38-1; 8-*endo*-**9**, 88106-39-2; 8-*exo*-**9**, 88106-40-5; 8-*endo*-**10**, 88195-51-1; 8-*exo*-**10**, 88195-53-3; (+)-**11**, 88195-52-2; $OC(CO_2Et)_2$, 609-09-6; diethyl (*R*,*R*)-(+)-tartrate, 87-91-2.

α-Amino Acids as Chiral Educts for Asymmetric Products. A General Synthesis of D-α-Amino Acids from L-Serine

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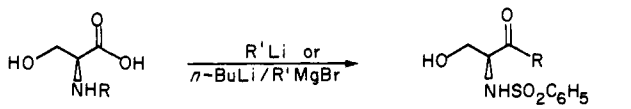
Abstract: A short and chirally efficient synthesis of four D-α-amino acids is described with L-serine as the chiral educt. The key C–C bond-forming reactions are the aminoacylations of organometallics with the lithium salt of *N*-(phenylsulfonyl)-L-serine (**2**) to give optically pure N-blocked α-amino ketones. Reduction of the carbonyl group to carbinol or methylene followed by oxidation of the hydroxymethyl to carboxyl gives the N-blocked D-amino acids. The examples investigated (norleucine, α-aminopimelic acid, DOPA, and allothreonine) demonstrate the broad applicability of the method.

The preparation of enantiomerically pure compounds is an increasingly important challenge in modern organic synthesis. To meet this challenge the synthetic chemist must rely on the "chiral pool" of organic substrates, either through their direct use or as inducing agents. While the natural L-α-amino acids are readily available, inexpensive members of this "chiral pool", the D-α-amino acids are in general rare and expensive materials. The most frequently described preparations of D-amino acids proceed either by resolution of a racemic mixture[2-4] or by asymmetric induction using a chiral auxiliary reagent.[5,6] These methods suffer from experimental unpredictability, the need for often expensive resolving agents or chiral auxiliary reagents, lack of complete diastereoselection, and tedious recovery or recycle processes.

Because the D-amino acids show great promise as precursors to biologically important compounds such as peptide analogues,[7-9]

Scheme I



1, R = H
2, R = $SO_2C_6H_5$

3a, R = R' = $CH_2CH_2CH_3$
b, R = $(CH_2)_4OH$, R' = $(CH_2)_4OTMS$
c, R = R' = 3,4-dimethoxyphenyl
d, R = R' = CH_3

antibiotics,[10,11] and alkaloids,[12] we have developed a general D-amino acid synthesis which consistently leads to optically pure materials and requires no resolving agents or chiral auxiliary reagents. Our synthesis proceeds from inexpensive L-serine and utilizes the aminoacylation of organolithium or Grignard reagents as the key carbon–carbon bond-forming step.[13,14] Four examples have been chosen to demonstrate the generality of the method. These are D-norleucine,[15] D-α-aminopimelic acid,[16] D-DOPA (D-

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