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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of 1-25; X-ray experimental description, non-hydrogen atomic parameters, anisotropic thermal parameters, hydrogen atom parameters, bond distances, bond angles, and endocyclic torsion angles; and Schemes I-III describing details of fractionation of compounds 1-25 (61 pages). Ordering information is given on any current masthead page.

A Short Synthesis of (±)-β-Isocomene

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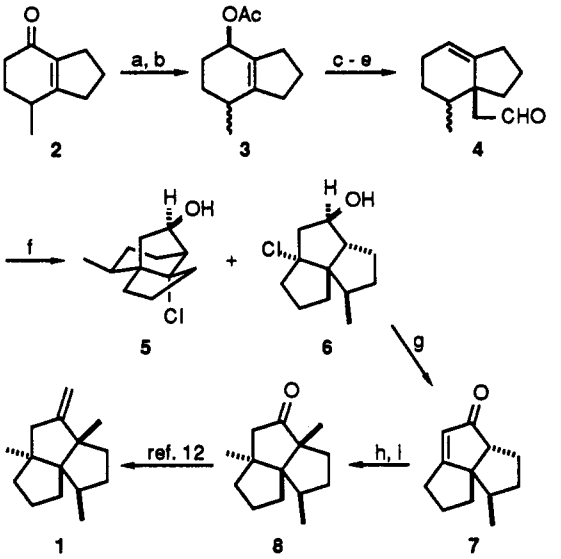
A strategy in which a Prins reaction is followed by a ring contraction has been used to synthesize (±)-β-isocomene efficiently.

Large numbers of triquinane natural products have been isolated, and efforts directed toward their synthesis have greatly expanded methodology for the construction and manipulation of cyclopentanes.[3] We report here a contribution to this field in which an intramolecular Prins reaction[4] followed by a ring contraction is applied to the synthesis of (±)-β-isocomene (1).[5]

The known[6] enone **2**, prepared[7] from cyclopentanone was reduced to give an inseparable 1:1.9 mixture of cis and trans alcohols in 95% yield.[8] Acetylation, Ireland ester enolate Claisen rearrangement,[9] and reduction afforded a 1:2 mixture of primary alcohols in 85% yield. Swern oxidation[10] gave an 84% yield of aldehydes **4** as an inseparable 1:2 mixture of diastereomers.

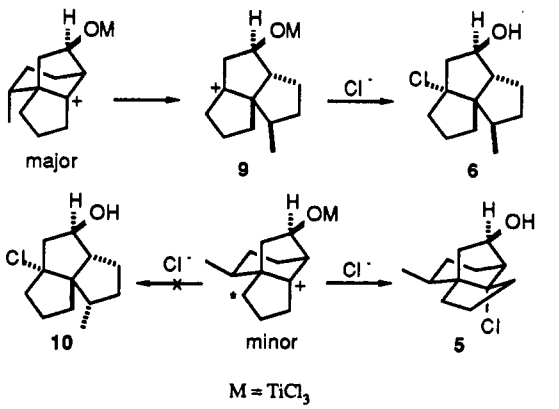
In the key step,[11] 1 equiv of a 1 M solution of $TiCl_4$ in CH_2Cl_2 was added to a 0.1 M solution of aldehydes **4** in

Scheme I[a]



[a] Key: (a) LAH, Et_2O, -78 °C; (b) Ac_2O, py; (c) LDA, TBDMSCl, THF, HMPA, -78 °C → reflux; (d) LAH, Et_2O, 0 °C; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -41 °C; (f) $TiCl_4$, CH_2Cl_2, -78 °C; (g) PCC, CH_2Cl_2; DBU, THF; (h) LDA, MeI, -78 °C → RT; (i) Me_2CuLi, Et_2O, 0 °C.

Scheme II



CH_2Cl_2 at -78 °C. Reaction was immediate and complete, giving a clear, slightly yellow solution, which after being warmed to 0 °C and quenched with water afforded a 1:2.3

(1) Bristol-Myers/Squibb fellowship recipient 1990-93.
(2) NSF Research Experiences for Undergraduates in Chemistry Program participant, Summer 1990.
(3) Hudlicky, T.; Rulin, F.; Lovelace, T.; Reed, J. In *Studies in Natural Product Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1989; Vol. 3, pp 3-72.
(4) For some examples of the application of intramolecular Prins reactions in cyclizations see: Marshall, J. A.; Wutts, P. G. M. *J. Am. Chem. Soc.* **1978**, *100*, 1627. Marshall, J. A.; Andersen, N. H.; Johnson, P. C. *J. Org. Chem.* **1970**, *34*, 186. Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014.
(5) (a) Oppolzer, W.; Battig, K.; Hudlicky, T. *Tetrahedron Lett.* **1981**, *37*, 4359. (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82. (c) Ranu, B. C.; Kavka, M.; Higgs, L. A.; Hudlicky, T. *Tetrahedron Lett.* **1984**, 2447. (d) Tobe, Y.; Yamashita, T.; Kakiuchi, K.; Odaria, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 898.
(6) Smith, A. B.; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845. Wexler, B. A. Ph.D Dissertation, University of Pennsylvania, 1982.
(7) Although previously prepared from the pyrrolidine enamine of cyclopentanone (see ref 6), the following procedure was found to be less tedious (see Experimental Section for details): Reaction of 2-propenylmagnesium bromide with cyclopentanone at -78 °C for 5 h in THF gave after vacuum distillation a 50% yield of tertiary alcohol. Dehydration by distillation from DMSO gave the corresponding diene in 87% yield. Heating the diene in neat 1-cyanovinyl acetate (5 equiv, containing 5% *tert*-butyl catechol) to 80 °C for 48 h afforded the Diels-Alder adduct in 73% yield. Hydrolysis (K_2CO_3, MeOH, rt, 2 h) gave enone **2** in 81% yield.
(8) Other reducing agents (i.e., sodium borohydride and L-Selectride (Aldrich)) were employed with similarly disappointing results.
(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(10) Manusco, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(11) (a) For a related Prins reaction that does not involve a 1,2 migration see: Anderson, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144. (b) See also: Kretschmar, H. C.; Barneis, Z. J.; Erman, W. F. *Tetrahedron Lett.* **1970**, 37.

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mixture of chloro alcohols **5**[12] and **6** in 95% yield. Intriguingly, *only the desired trans isomer undergoes the 1,2 migration.* Moreover, isomers **5** and **6** are readily separable by flash chromatography.[13]

There are two plausible explanations for the different behavior of the two diastereomers. The first is that the 1,2 migration of the minor diastereomer is hindered by interference between the methyl group and the starred methylene in Scheme II, whereas in the major diastereomer the progress of the methyl group during the 1,2 migration should be relatively unimpeded. The second explanation is that the methyl group in structure **10** interferes sterically with approach of the chloride ion.

Conversion of the diastereomerically pure chloro alcohol **6** to isocomene was straightforward. Oxidation and elimination gave a 98% yield of enone **7**.[14] Methylation of the kinetic enolate (87% yield) and addition of lithium dimethyl cuprate (89% yield) afforded the ketone **8**,[15] which Tobe et al.[5d] have converted to β-isocomene (**1**) by a Wittig reaction (98% yield). The ^1H NMR and ^{13}C NMR spectral data of (±)-β-isocomene synthesized in this way matched those reported in the literature.[16] Thus, (±)-β-isocomene has been prepared from the readily available enone **2** in 34% overall yield (10 steps) and in 12% overall yield from cyclopentanone. Despite the production of a diastereomeric mixture upon reduction of enone **2**, this synthesis of β-isocomene is the most efficient[17] in terms of overall yield and compares favorably in total number of steps with the exception of work by Pirrung.[5b] Further studies of this novel cyclization/ring contraction sequence will be published separately.

Experimental Section

^1H and ^{13}C NMR spectra were recorded at 400 and 75 MHz, respectively, in $CDCl_3$. IR spectra were recorded in $CHCl_3$. Reactions were performed under Ar using dried glassware.

1-(1-Methylethenyl)cyclopentanol (11). To a stirred mixture of magnesium turnings (16.6 g, 684 mmol) in THF was added a solution of 2-bromopropene (49.7 g, 411 mmol) in 70 mL of THF at a rate which maintained gentle reflux. The mixture was refluxed for an additional 30 min then cooled to −78 °C. A solution of cyclopentanone (28.78 g, 342 mmol) in 100 mL of THF was added dropwise, and stirring was continued at −78 °C for 5 h. The mixture was warmed to 0 °C, poured into ice-cold saturated aqueous NH_4Cl (500 mL), and extracted with ether (4 × 200 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated to give 38.1 g of crude alcohol **11** as a brown oil. Vacuum distillation (30–60 °C (0.45 mmHg)) of 11.9 g of this oil provided 7.68 g (60.9 mmol, 57%) of alcohol **11**: IR 3596, 3448, 1643 cm^{-1}; ^1H NMR δ 5.01 (sextet, J = 0.8 Hz, 1 H), 4.79 (quintet, J = 1.5 Hz, 1 H), 1.54–1.94 (m, 9 H), 1.81 (dd, J = 1.5, 0.8 Hz, 3 H).

1-(1-Methylethenyl)cyclopentene (12). Distillation (105–110 °C) of 19.8 g (157 mmol) of alcohol **11** at atmospheric pressure through a Vigreux column, from 67 mL (6 equiv) of DMSO, gave 14.8 g (137 mmol, 87%) of diene **12**: IR 1628, 1596 cm^{-1}; ^1H NMR δ 5.75 (br s, 1 H), 4.88 (br s, 1 H), 4.85 (br s, 1 H), 2.45 (m, 4 H), 1.92 (s, 3 H), 1.90 (m, 2 H).

2,3,5,6,7,7a-Hexahydro-4-methyl-7-acetoxy-7-cyano-1*H*-indene (13). A solution of 2.0 g (18.3 mmol) of diene **12**, 10.1 g (91.7 mmol) of 1-cyanovinyl acetate, and 0.50 g of *tert*-butyl catechol was heated to 90 °C for 48 h. Vacuum distillation afforded 7.3 g of 1-cyanovinyl acetate (40 °C (0.04 mmHg)) and 3.8 g of crude cyano acetate **13**. Flash chromatography (15% EtOAc/hexanes) gave 2.95 g (13.4 mmol, 74%) of cyano acetate **13**.

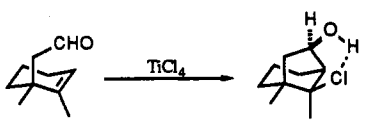
2,3,4,5,6,7-Hexahydro-7-methyl-1*H*-inden-4-one (2). A mixture of 1.0 g (4.56 mmol) of cyano acetate **13** and 0.69 g (5.03 mmol) of K_2CO_3 in 23 mL methanol was stirred at rt for 2 h; the mixture was poured into 100 mL water and extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were washed once with water, and the aqueous layer was back-extracted three times with CH_2Cl_2. This sequence was repeated with brine. The organic layers were concentrated to afford 0.88 g of crude oil. Flash chromatography (30% ether/hexanes) gave 554 mg (3.69 mmol, 81%) of enone **2** as a colorless oil: IR 1656 cm^{-1}; ^1H NMR δ 2.64 (m, 1 H), 2.39–2.53 (m, 5 H), 2.30 (ddd, J = 16.8, 10.8, 4.8 Hz, 1 H), 2.08 (ddt, J = 13.4, 6.3, 4.8 Hz, 1 H), 1.85 (m, 2 H), 1.67 (dddd, J = 13.2, 10.8, 8.4, 4.7 Hz, 1 H), 1.02 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 198.03, 169.54, 136.80, 36.68, 35.65, 31.85, 31.77, 29.37, 21.56, 18.31.

2,3,4,5,6,7-Hexahydro-7-methyl-1*H*-inden-4-ol (15). To a solution of 0.80 g (21.2 mmol) of $LiAlH_4$ in 212 mL of ether cooled to −78 °C was added 3.19 g (21.2 mmol) of enone **2**. The mixture was allowed to warm to 0 °C, and 0.8 mL of water, 0.8 mL of 15% aqueous NaOH, and 2.4 mL of water, successively, were added. Stirring was continued until the mixture had became white then filtered through Celite and concentrated to give 3.07 g (20.2 mmol, 95%) of alcohols **15** as a 1:1.9 cis/trans mixture of isomers: IR 3606, 3447, 3011, 2932, 2848, 1458, 1446, 1375, 1297, 1233, 1046, 994, 974, 903 cm^{-1}; ^1H NMR δ 4.17 and 4.13 (m, 1 H) 2.51–2.65 (m, 1 H), 2.36–2.51 (m, 1 H), 2.05–2.33 (m, 3 H), 1.88 (m, 0.5 H), 1.62–1.92 (m, 4 H), 1.53 (m, 1 H), 1.40 (m, 1 H), 1.27 (m, 0.5 H), 1.02 and 0.96 (d and d, J = 0.5 Hz for both, 3 H, ratio 1.9:1); ^{13}C NMR δ 144.17, 143.33, 135.80, 135.40, 67.01, 65.99, 34.00, 33.73, 33.35, 32.59, 31.28, 31.23, 31.16, 30.63, 28.82, 27.66, 21.83, 21.70, 19.22, 18.91; MS (EI) m/z 152 (M^+), 134, 124, 110, 93, 67; HRMS (EI) calcd for $C_{10}H_{16}O$ 152.1201, found 152.1189.

2,3,4,5,6,7-Hexahydro-4-acetoxy-7-methyl-1*H*-indene (3). A solution of (3.06 g, 20.10 mmol) of alcohols **15** and 6 mL of acetic anhydride in 30 mL of pyridine was stirred at rt for 12 h. The solution was diluted with 6 mL of water followed by ether and then washed with 1 N HCl (three times) until the aqueous layer remained acidic. The organic layers were washed once with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated to give 3.72 g (19.15 mmol, 98%) of acetates **3**, in a 1:2.0 cis/trans ratio: IR 3008, 2958, 2934, 2849, 1723, 1458, 1447, 1372, 1253, 1019, 959 cm^{-1}; ^1H NMR δ 5.34 and 5.30 (m and m, 1 H), 2.30–2.52 (m, 2 H), 2.16–2.28 (m, 2 H), 2.05 (s, 3 H), 2.01 (m, 1 H), 1.67–1.91 (m, 4 H), 1.61 (m, 1 H), 1.32 (m, 1 H), 1.03 and 0.97 (d and d, J = 7.1, 7.0 Hz, 3 H, ratio 2.0:1); ^{13}C NMR δ 171.10, 171.05, 146.80, 145.88, 132.26, 131.90, 69.45, 58.59, 34.03, 33.72, 33.53, 32.87, 31.00, 30.36, 28.63, 28.18, 28.00, 27.34, 21.64, 21.55, 21.43, 21.33, 19.04, 18.71; MS (EI) m/z 194 (M^+), 134, 119, 106, 91, 43; HRMS (EI) calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1291.

Silyl Ketene Acetal Formation and in Situ Ireland–Claisen Rearrangement of Acetate (3). To 19.8 mL of THF cooled to −78 °C were successively added 2.9 mL (7.72 mmol) of a 2.67 M solution of nBuLi in hexanes, 1.04 g (10.30 mmol) of diisopropylamine, 2 mL of HMPA, 1.0 g (5.15 mmol) of acetates **3**, and a solution of 1.24 mg (8.24 mmol) of TBDMSCl in 1 mL

(12) Structural assignment of isomer **5** is based on the following: The corresponding ketone did not readily eliminate under acidic or basic conditions, as did the ketone derived from the major isomer **6**, ruling out an angular triquinane ring skeleton. The expected stereochemistry (Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970 and ref 11a) of the carbinol center is confirmed by the absence of an observable ^1H coupling constant between the carbinol proton and that of the bridgehead, the dihedral angle being 90° for this ring skeleton and carbinol stereochemistry. The chloride stereocenter was assigned based on the absence of a strong hydrogen bond from the alcohol to the chloride in the ^1H NMR and IR, as was observed in a related system (Lee, H.-H.; Kennedy, R. M., unpublished results):



(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(14) Enone **7** has previously been identified as a potential synthetic precursor to isocomene. Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025.

(15) Ketone **8** showed identical ^1H NMR and IR spectra to that reported previously. Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82.

(16) (a) Bohlman, F; Van, N. L.; Pham, T. V. C.; Jucupovic, J.; Schuster, A.; Zabel, V.; Watson, W. H. *Phytochem.* **1979**, *18*, 1831. Also see ref 5c.

(17) Reference: 5a, 10 steps, 1%; 5b, five steps, 9.3%; 5c, 15 steps, 3.3%; 5d, 12 steps, 7.7%.

of THF. The solution was allowed to warm to rt and then refluxed for 24 h. The solution was diluted with hexanes, washed three times with water, washed once with half-saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered through Celite, and concentrated to give 2.2 g of crude silyl esters **16**; MS (EI) m/z 308 (M^+), 251, 135, 134, 75.

2,3,3a,4,5,6-Hexahydro-3a-(2-hydroxyethyl)-4-methyl-1*H*-indene (17). The crude silyl ester **16** was added to a solution of $LiAlH_4$ (781 mg, 20.59 mmol) in 52 mL of ether cooled to 0 °C. The mixture was stirred at rt for 10 min and recooled to 0 °C. To the mixture were successively added the following: 0.78 mL of water, 0.78 mL of 15% aqueous NaOH, and 2.34 mL of water. Stirring continued until the mixture became white. $MgSO_4$ was added, and the mixture was filtered and concentrated to give 2.15 g yellow oil. Flash chromatography (40% Et_2O/hexanes) afforded 770 mg (4.27 mmol, 83% from acetates **3**) of alcohols **17**, in a 1:2.2 cis/trans ratio, as a semicrystalline oil: IR 3620, 3462, 3011, 2959, 2843, 1463, 1437, 1377, 999 cm^{-1}; ^1H NMR δ 5.43 and 5.39 (m and m, 1 H), 3.68 (m, 2 H), 1.22–2.48 (m, 12 H), 0.96 and 0.83 (d, J = 7.0 Hz and d, J = 6.8 Hz, 3 H, ratio 2.2:1); ^{13}C NMR δ 147.23, 145.64, 118.77, 117.42, 61.63, 60.22, 45.44, 45.30, 40.13, 39.90, 39.70, 36.70, 32.34, 31.94, 31.29, 30.08, 27.05, 26.25, 25.25, 22.04, 21.06, 22.99, 17.45, 15.40; MS (EI) m/z 180 (M^+), 162, 147, 135, 119, 105, 91, 79, 67, 55, 41, 31, 28; HRMS (CI) calcd for ($C_{12}H_{20}O$ + H^+) 181.1592, found 181.1595.

2,3,3a,4,5,6-Hexahydro-3a-(2-oxoethyl)-4-methyl-1*H*-indene (4). To a solution of 786 mg (6.19 mmol) of oxalyl chloride in 8.25 mL CH_2Cl_2 at −41 °C was slowly added a solution of 967 mg (12.38 mmol) of DMSO in 0.9 mL of CH_2Cl_2. The solution was stirred for 10 min. A solution of 744 mg (4.13 mmol) of alcohols **17** in 1 mL of CH_2Cl_2 was added slowly, followed after 30 min by slow addition of 2.67 g (26.41 mmol) of Et_3N and then another 30 min of stirring. The mixture was allowed to warm to rt, diluted with 30 mL of EtOAc, washed with 1 N HCl which was back-extracted once with EtOAc, washed with saturated aqueous $NaHCO_3$ which was back-extracted once with ethyl acetate, dried ($MgSO_4$), and concentrated to afford 822 mg of crude aldehydes **4** in a 1:2.0 cis/trans ratio. Flash chromatography (4% Et_2O/hexanes) gave 615 mg (3.45 mmol, 84%) of aldehydes **4** and 21-mg recovery of alcohols **17**: IR 2962, 2934, 2880, 2842, 1713, 1463, 1438, 1378 cm^{-1}; ^1H NMR δ 9.75 (m, 1 H), 5.49 and 5.45 (m and m, 1 H), 1.22–2.46 (m, 13 H), 0.97 and 0.88 (d and d, J = 6.9, 6.8 Hz, 3 H, ratio 2.0:1); ^{13}C NMR δ 204.80, 203.99, 144.92, 143.21, 119.47, 118.38, 50.67 (two peaks), 46.96, 45.66, 39.74, 39.17, 32.96, 32.72, 29.96, 29.53, 27.01, 25.58, 25.31, 21.46, 20.82, 20.32, 17.47, 14.99; HRMS (EI) calcd for $C_{12}H_{18}O$ 178.1358, found 178.1353.

(3a*S,4*S**,7a*S**,8*R**)-Octahydro-7a-chloro-4-methyl-3a,7-ethano-3a*H*-inden-8-ol (5) and (3a*R**,5*R**,8*R**,8a*S**)-Decahydro-3a-chloro-8-methylcyclopenta[*c*]pentalen-5-ol (6).** To a solution of 615 mg (3.45 mmol) of aldehydes **4** in 51 mL of CH_2Cl_2 at −78 °C was added 3.8 mL of a 1 M solution of $TiCl_4$ in CH_2Cl_2. The resulting slightly yellow solution was stirred for 15 min at −78 °C and allowed to warm to 0 °C. To the solution was added 60 mL of water. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were dried ($MgSO_4$), filtered through Celite, and concentrated to afford 820 mg of a mixture of chloro alcohols **5** and **6** in a 1:2.28 ratio. Careful flash chromatography (CH_2Cl_2) gave 493 mg (2.30 mmol, 66.5%) of the major isomer **6**, mp 52–54 °C, as a slowly crystalline solid and 205 mg (0.95 mmol, 27.5%) of the minor isomer **5** as a readily crystalline solid, mp 105–106 °C (94% total yield of chloro alcohols). Major isomer: IR 3610, 3455, 3010, 2958, 2872, 1459, 1450, 1377, 1119, 1066, 1005, 949 cm^{-1}; ^1H NMR δ 3.94 (td, J = 7.1, 5.7 Hz, 1 H), 2.48 (dd, J = 13.8, 5.8 Hz, 1 H), 2.32 (dddd, J = 13.2, 6.4, 3.0, 1.3 Hz, 1 H), 2.25 (sept, J = 6.2 Hz, 1 H), 2.08 (dd, J = 13.7, 7.14 Hz, 1 H), 2.03 (ddd, J = 13.2, 10.7, 7.0, 1 H), 2.00 (br s, 1 H), 1.60–1.95 (m, 6 H), 1.36 (m, 3 H), 1.00 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 82.90, 76.60, 65.55, 62.28, 52.69, 45.45, 41.45, 36.56, 32.03, 28.79, 22.68, 15.74. Anal. Calcd for $C_{12}H_{19}OCl$: C, 67.12; H, 8.92. Found: C, 67.12; H, 8.95. Minor isomer: IR 3608, 3450, 2957, 2871, 1463, 1378, 1293, 1254, 1078, 1041, 1024, 973, 900, 873, 828, 580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (dd, J = 8.7, 3.5 Hz, 1 H), 2.82 (ddd, J = 14.6, 10.6, 8.6 Hz, 1 H), 2.29 (br t, J = 3.3 Hz, 1 H), 2.18 (dd, J = 14.6, 9.1, 2.3 Hz, 1 H), 2.13 (dd, J = 14.2, 8.9 Hz, 1 H), 2.01–2.13 (m, 2 H), 1.95 (m, 1 H), 1.81 (m, 1 H), 1.73 (br s, 1 H), 1.69 (ddd, J = 13.0, 9.2, 3.4 Hz, 1 H), 1.59 (ddd, J = 12.8, 11.1, 6.8 Hz, 1 H), 1.44 (m, 2 H), 1.19 (dd, J = 14.5, 3.4 Hz, 1 H), 0.76 (m, 1 H), 0.76 (d, J = 6.7 Hz, 3 H); ^1H NMR (CD_3OD) δ 3.94 (td, J = 8.7, 3.6 Hz, 1 H), 2.80 (ddd, J = 14.6, 10.6, 8.6 Hz, 1 H), 2.15 (br t, J = 3.3 Hz, 1 H), 2.05 (dd, J = 14.4, 8.6 Hz, 1 H), 1.90–2.04 (m, 3 H), 1.83 (m, 1 H), 1.74 (m, 1 H), 1.62 (ddd, J = 12.4, 9.2, 3.3 Hz, 1 H), 1.50 (ddd, J = 12.5, 11.2, 6.7 Hz, 1 H), 1.35 (m, 2 H), 1.10 (dd, J = 14.3, 3.4 Hz, 1 H), 0.77 (qd, J = 13.1, 6.6 Hz, 1 H), 0.70 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 89.28, 73.58, 58.84, 51.46, 39.95, 38.10, 34.67, 31.23, 26.99, 26.77, 19.83, 17.21. Anal. Calcd for $C_{12}H_{19}OCl$: C, 67.12; H, 8.92. Found: C, 67.14; H, 9.02.

(5a*R,8*R**8a*S**)-1,2,3,5,5a,6,7,8-Octahydro-8-methylcyclopenta[*c*]pentalen-5-one (7).** To 829 mg (3.861 mmol) of major chloro alcohol **5** in 39 mL of CH_2Cl_2 was added 2.08 g (9.653 mmol) of pyridinium chlorochromate. After 2 h of stirring, the mixture was filtered through silica gel and washed through with ether. After solvent removal, 9 mL of THF and 1,4-diazabicyclo[5.4.0]undec-7-ene (DBU) (9 drops) was added. The mixture was filtered through silica gel with ether washings and concentrated to give 664 mg (3.77 mmol, 98%) of enone **7**, as an oil: IR 3020, 2965, 2872, 1686, 1629, 1454, 1227, 1210, 867, 801, 790, 736, 732, 664 cm^{-1}; ^1H NMR δ 5.81 (m, 1 H), 2.51–2.68 (m, 2 H), 2.41 (br d, J = 8.9 Hz, 1 H), 2.12 (dd, J = 12.7, 6.1 Hz, 1 H), 1.80–2.05 (m, 5 H), 1.61 (m, 1 H), 1.38 (m, 2 H), 0.97 (d, J = 7.2 Hz, 3 H); ^1H NMR (CD_3OD) δ 5.73 (t, J = 1.6 Hz, 1 H), 2.62 (m, 1 H), 2.53 (dtq, J = 18.3, 7.0, 1.0 Hz, 1 H), 2.35 (br d, J = 8.7 Hz, 1 H), 2.10 (m, 1 H), 1.96 (m, 2 H), 1.84 (m, 2 H), 1.74 (ddt, J = 12.8, 6.4, 2.0 Hz, 1 H), 1.52 (septet, J = 6.3 Hz, 1 H), 1.32 (m, 2 H), 0.94 (d, J = 7.2 Hz, 3 H); ^{13}C NMR δ 214.52, 194.72, 124.34, 64.46, 57.61, 36.69, 32.45, 30.36, 26.40, 25.62, 24.23, 16.15; MS (EI) m/z 176 (M^+), 161, 148, 134, 120, 105, 91, 77, 65, 53, 41, 31, 28; HRMS (EI) calcd for $C_{12}H_{16}O$ 176.1201, found 176.1219.

(5a*R,8*R**,8a*S**)-1,2,3,5,5a,6,7,8-Octahydro-5a,8-dimethylcyclopenta[*c*]pentalen-5-one (18).** A 2.17-mL (5.75-mmol) portion of *n*-BuLi (2.65 M in hexanes) was added to 48 mL of THF cooled to −78 °C, followed by 630 mg (6.23 mmol) of diisopropylamine. A solution of 845 mg (4.794 mmol) of enone **7** in THF (3 mL) was added dropwise. The solution was allowed to warm to 0 °C, 3.40 g (24.0 mmol) MeI was added, and the solution was stirred for 2 h. The solution was diluted with ether (40 mL) and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with ether. The organic layers were dried with $MgSO_4$, concentrated, filtered through silica gel with ether washings, and again concentrated to give 938 mg of a yellow oil. Flash chromatography (30% Et_2O/hexanes) gave 793 mg (4.167 mmol, 87%) of crystalline enone **18**: mp 56–57 °C; IR 3014, 2965, 2871, 1960, 1630, 1453, 1259, 1128, 869 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (t, J = 1.6 Hz, 1 H), 2.48–2.70 (m, 2 H), 1.86–2.05 (m, 5 H), 1.56 (td, J = 13.0 and 6.0 Hz, 1 H), 1.44 (septet, J = 6.4 Hz, 1 H), 1.26 (m, 3 H), 1.02 (s, 3 H), 0.96 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 216.52, 192.37, 123.04, 67.01, 57.37, 36.69, 35.15, 29.74, 27.48, 25.55, 23.81, 19.47, 16.26. Anal. Calcd for $C_{13}H_{18}O$: 82.06; H, 9.53; found C, 81.99; H, 9.66.

(3a*R,5a*R**,8*R**,8a*S**)-Decahydro-3a,5a,8-trimethylcyclopenta[*c*]pentalen-5-one (8).** A solution of 0.85 mL (2.102 mmol) of MeLi (2.46 M in ether) was added to 200 mg (1.05 mmol) of CuI in 5.3 mL of ether cooled to 0 °C. The mixture was stirred (10 min) until the yellow solid dissolved, to give a slightly cloudy solution. This solution was added dropwise to 100 mg (0.526 mmol) of enone **18** in 5.3 mL of ether cooled to 0 °C. A solution of 10% NH_4Cl (adjusted to pH 8 with NH_4OH) was added, and stirring was continued until a deep blue aqueous solution resulted. The aqueous layer was extracted three times with ether. The organic layers were dried with $MgSO_4$ and concentrated to give 116 mg of a solid. Flash chromatography (15% EtOAc/hexanes) gave 96.2 mg (0.468 mmol, 89%) of ketone **8** as a white crystalline solid: mp 147–148 °C; IR 2962, 2874, 1724, 1458, 1411, 1380, 1268, 1148, 1103 cm^{-1}; ^1H NMR δ 2.41 (d, J = 17.3 Hz, 1 H), 2.16 (d, J = 17.1 Hz, 1 H), 2.12 (m, 1 H), 1.53–1.78 (m, 8 H), 1.29–1.48 (m, 3 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 0.99 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 222.94, 64.89, 59.04, 50.85, 46.41, 42.22, 40.82, 39.56, 39.93, 29.02, 23.53, 23.15, 20.70, 17.86. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.81; H, 10.86.

(±)-β-Isocomene (1). Wittig reaction of ketone **8**[5b] (23.7 mg) afforded β-isocomene as the sole product. Column chromatography with pentane to remove the last traces of Ph_3PO and toluene

gave 14.4 mg of pure 1: ^{1}H NMR ($CDCl_3$) δ 4.61 (m, 1 H), 4.59 (quintet, J = 1.4 Hz, 1 H), 2.32 (ddd, J = 14.4, 2.4, and 1 Hz), 2.08 (d, J = 14.4 Hz, 1 H), 1.97 (sextet, J = 7.2 Hz, 1 H), 1.90–1.68 (m, 10 H), 1.07 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 162.23, 100.64, 54.76, 49.36, 47.99, 42.80, 41.66, 40.42, 34.54, 30.27, 24.19, 24.00, 23.40, 17.98.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds 1–7, 15, and 17 (17 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of 1,3-Amino Alcohols and 1,3-Amino Ketones

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syn,anti-N-Alkyl-1,3-amino alcohols **2** with three chiral centers are synthesized with high stereoselectivity by reduction of the corresponding *anti-N*-acylamino ketones **1** with $LiAlH_4/TiCl_4$. The intermediate *N*-acylamino alcohols **3** can be isolated when $DIBALH/ZnCl_2$ is used instead of the prior reducing system. Cyclic models are proposed to explain the steric course of the reaction in both cases. On the other hand, hydrolysis of tetrahydropyrimidines **8** with 1 N HCl at 25 °C leads to *syn*-1,3-amino ketones **9** with high stereoselectivity. Several reducing reagents and conditions are tested in the conversion of *syn*-**9** into the subsequent 1,3-amino alcohols. $DIBALH/ZnCl_2$ gives the best results in the last reaction leading to *syn,syn*-1,3-amino alcohols **10** as practically a single diastereoisomer.

Introduction

Among 1,3-difunctionalized compounds, the 1,3-amino alcohol fragment is one of the most important target structures because of the pharmacology of these substances and because this functionality is found in several antibiotics[1] and other biologically active natural products.[2] Therefore, the synthesis of these molecules has been of great interest,[1a,3] and several reduction methods have been widely used for this purpose.[4,5] In this context, preparation of 1,3-amino alcohols by reduction of β-amino carbonyl compounds is the most frequently employed methodology.[4,6]

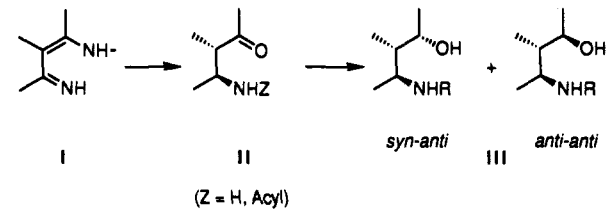
In our research group 4-amino-1-aza 1,3-dienes I have been used as starting materials for several 1,3-difunctionalized compounds like 1,3-amino ketones[7] and 1,3-diamines.[7a] The former have two chiral centers in the molecule and are obtained with high stereoselectivity as mixtures of two diastereoisomers from which only the anti isomer (the major component) could be isolated (II in Scheme I). We reported diastereo-[7b] and enantioselective[8] synthesis of 1,3-amino alcohols III with three chiral centers by reduction of 1,3-amino- and 1,3-amido ketones II. In this synthesis the syn,anti and anti,anti diastereoisomers were obtained (Scheme I).

The reduction of 1,3-amino ketones II is highly stereoselective only with unsubstituted amino ketones (Z = H) which give the syn,anti isomer as the major product. The stereoselectivity sensibly decreases for *N*-acylamino ketones (II, Z = Acyl).[7b] In this paper we report our studies to improve the diastereoselective synthesis of 1,3-amino alcohols having three chiral centers from *anti-N*-acyl-1,3-amino ketones[9] and to the synthesis of *syn*-1,3-amino ketones and the subsequent 1,3-amino alcohols.

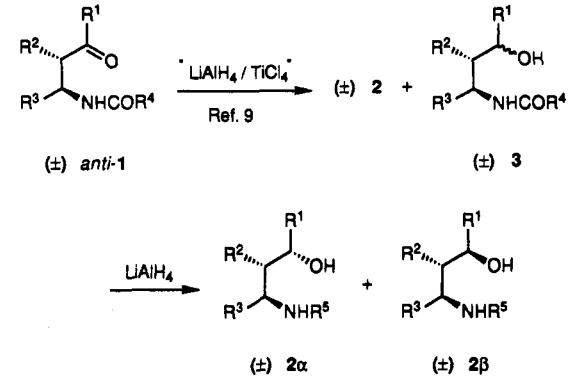
Results and Discussion

Synthesis of *N*-Alkyl-1,3-amino Alcohols 2. (A) Reduction of *anti*-1,3-Amino Ketones 1 with $LiAlH_4/TiCl_4$. In our preliminary work on the synthesis of 1,3-amino alcohols, as pointed out above, we obtained low-to-moderate diastereoselectivities when *N*-acylamino ketones were used with $LiAlH_4$ as reducing agent. In order to improve the stereoselectivity in the reduction process,

Scheme I



Scheme II



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