Notes

Bridged Systems via Radical Cyclization Reactions. Stereospecific Synthesis of Chiral Tricyclo[6.2.1.0^{1,5}]undecanes[1]

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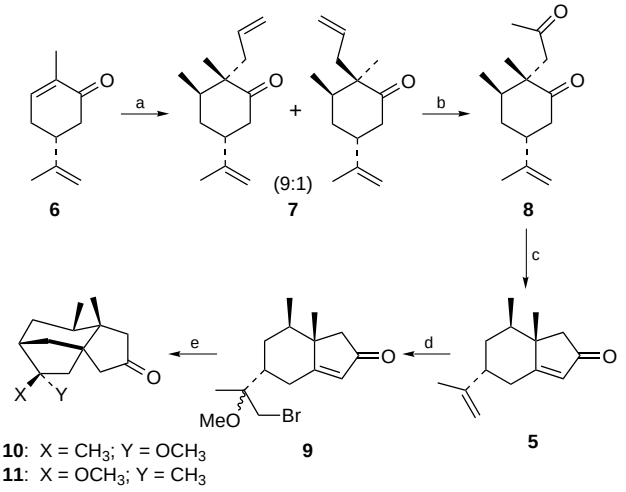
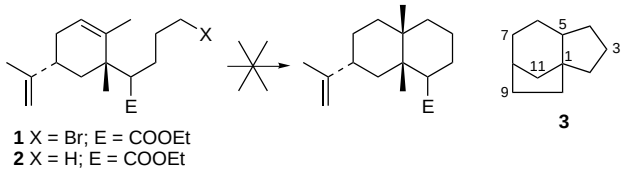
Received March 1, 1996

The application of radical-mediated cyclizations and annulations in organic synthesis has grown in importance steadily over the years to reach the present status where they are now routinely used in the strategy-level planning.[2] The presence of a quaternary carbon atom is frequently encountered in terpenoid natural products, and it often creates a synthetic challenge when two or more quaternary carbon atoms are present in a contiguous manner.[3] Even though creation of a quaternary carbon atom by employing a tertiary radical is very facile, creation of a quaternary carbon atom (or a spiro carbon atom) via radical addition onto a fully substituted olefinic carbon atom is not that common but of synthetic importance. For example, the primary radical derived from the bromide **1** failed to cyclize to generate the two vicinal quaternary carbon atoms and resulted in only the reduced product **2**.[4] The tricyclic carbon framework tricyclo[6.2.1.0^{1,5}]undecane **(3)** is present in a number of sesquiterpenoids *e.g.* zizzanes, prelacinanes, etc.[5] In continuation of our interest in the radical-mediated construction of chiral-bridged systems starting from the readily available monoterpene *R*-carvone,[6] herein we describe a stereospecific construction of the title chiral tricyclic bridged system via the radical cyclization-mediated creation of a spiro carbon atom vicinal to an existing quaternary carbon atom, in a stereospecific manner.

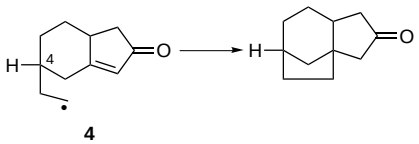
Scheme 1[a]



[a] (a) (i) $(CH_3)_2CuLi$, Et_2O; (ii) $CH_2{=}CHCH_2Br$, HMPT; (b) $PdCl_2$, CuCl, O_2, DMF, H_2O; (c) KOH, CH_3OH, H_2O; (d) NBS, CH_2Cl_2, CH_3OH; (e) $^nBu_3SnH$, AIBN, C_6H_6.



It was anticipated that a 5-*exo*-trig cyclization of a radical, *e.g.* **4**, onto an activated olefin would lead to the stereospecific construction of the tricyclo[6.2.1.0^{1,5}]-undecanes via the creation of the spiro carbon atom, wherein the stereospecificity is controlled by the stereochemistry of the ethyl side chain at C-4. For the



generation of the requisite radical precursor, the chiral hydrindenone **5** was chosen as the starting material.[7] The synthetic sequence starting from (*R*)-carvone **6** is given in Scheme 1. Thus a highly stereoselective addition of lithium dimethylcopper to enone **6** followed by trapping of the intermediate enolate with allyl bromide generated a 9:1 epimeric mixture of the allylated ketone **7**. Besides the conformational reasoning, the stereostructure of the major products rests, secured from its elaboration[7] to a precursor of the sesquiterpene homogynolide-A,[8] whereas that of the minor isomer was assigned to spectral

(1) Chiral synthons from carvone Part 21. For part 20, see Srikrishna, A.; Viswajanani, R. *Indian J. Chem. Sec. B* **1996**, *35B*, 521.

(2) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*: Pergamon Press: Oxford, 1986. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (c) Hart, D. J. *Science* **1984**, *223*, 883. (d) Giese, B., Ed. Selectivity and Synthetic Applications of Radical Reactions (Tetrahedron Symosia-in-print). *Tetrahedron* **1985**, *41*, 3887−4302. (e) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (f) Curran, D. P. *Synthesis* **1988**, 417; 489. (g) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361. (h) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (i) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (j) Curran, D. P. *Synlett* **1991**, 63.

(3) (a) ApSimon, J. W.; Heathcock, C. H.; Hopper, J. W.; Taub, D.; Thomas, A. F. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; 1973; Vol. 2. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, M. C.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1983; Vol. 5.

(4) Srikrishna, A.; Viswajanani, R. *Tetrahedron Lett.* **1996**, *37*, 2863.

(5) (a) Reference 3b, pp 473−483. (b) Fukushi, Y.; Yajima, C.; Mizutani, J. *Tetrahedron Lett.* **1994**, *35*, 8809. (c) Carrol, P. J.; Ghisalberti, E. L.; Ralph, D. E. *Phytochemistry* **1976**, *15*, 777. (d) Ghisalberti, E. L.; White, A. H.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1300. (e) Selvakumar, N.; Subba Rao, G. S. R. *J. Chem. Soc., Chem. Commun.* **1994**, 1303.

(6) (a) Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883. (b) Srikrishna, A.; Sharma, G. V. R.; Hemamalini, P. *J. Chem. Soc., Chem. Commun.* **1990**, 1681. (c) Srikrishna, A.; Hemamalini, P. *Tetrahedron* **1992**, *48*, 9337. (d) Srikrishna, A.; Hemamalini, P.; Sharma, G. V. R. *J. Org. Chem.* **1993**, *58*, 2509. (e) Srikrishna, A.; Hemamalini, P.; Venkateswarlu, S. *Tetrahedron* **1994**, *50*, 8781.

(7) Srikrishna, A.; Reddy, T. J.; Nagaraju, S. *Tetrahedron Lett.* **1996**, *37*, 1679.

(8) Srikrishna, A.; Reddy, T. J. *Indian J. Chem. Sec. B* **1995**, *34B*, 844.

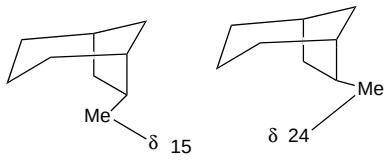
(9) All the four possible isomers of **7** were prepared in our lab.[7,8] The spectral comparisons were carried out on the pure diketones obtained after the Wacker oxidation.

(10) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975.

S0022-3263(96)00423-9 CCC: $12.00

comparison with the remaining two isomers prepared earlier.[8,9] Regiospecific oxidation of the olefinic moiety of allyl group in the dienone **7** using Wacker conditions ($PdCl_2$, CuCl, O_2, DMF, H_2O)[10] followed by purification on a silica gel column furnished the diketone **8**. Intramolecular aldol condensation transformed the diketone **8** into the hydrindenone **5**. The hydrindenone **5** was converted into the radical precursor, bromoenone **9**, by employing a regiospecific bromoetherification reaction.[11] Thus reaction of the hydrindenone **5** with *N*-bromosuccinimide (NBS) in methanol−methylene chloride medium furnished a diastereomeric mixture of the bromoenone **9**. After different conditions were briefly explored, the radical cyclization reaction of the bromoenone **9** was carried out by slow addition of a benzene solution of a mixture of tri-*n*-butyltin hydride (1.1 equiv) and a catalytic amount of azobisisobutyronitrile (AIBN) to a refluxing benzene solution of the bromoenone **9** (overall concentration of $^nBu_3SnH$ 0.01 M) to furnish an epimeric mixture of the tricyclic ketones **10** and **11**, which was separated by silica gel column chromatography. The gross structure of the cyclized products **10** and **11** were derived from their comparable spectral data. The absence of olefinic proton and carbon resonances in the NMR spectra, the shift in the carbonyl absorption band to 1740 cm^{-1} in the IR spectra, and the downfield shift of carbonyl carbon resonances to δ 218.3 and 218.55 ppm in the ^{13}C NMR spectra due to a cyclopentanone carbonyl group clearly established the radical cyclization reaction. The presence of three quaternary (δ 84.2, 50.9, and 44.7), two methine (43.4 and 34.7), and five methylene (50.5, 48.9, 47.7, 33.2 and 32.5 ppm) aliphatic carbon atoms in the ^{13}C NMR spectrum (SEFT) on the product **11** (and similarly for the ketone **10**) established the regiospecificity in the cyclization as 5-*exo* mode, as the alternative 6-*endo* mode would have resulted in four each of methine and methylene and two quaternary carbon atoms. The stereochemical assignment at C-9 was derived from the downfield shift of the C-9 methyl carbon resonance (δ 26) in the ketone **10** when compared with that of the ketone **11** (17.5 ppm).

It was established[12,6a] that in the 6-methylbicyclo[3.2.1]-octanes, the *exo*- and the *endo* methyl carbons resonate in the range of δ24 and 15 ppm, respectively. The facile formation of the tricyclic compounds **10** and **11** from the bromide **9** is obviously due to the electrophilic nature of the enone. The axial orientation of the side chain in the preferred conformation of the intermediate radical might have further facilitated the cyclization.



In conclusion, we have achieved the synthesis of chiral tricyclo[6.2.1.$0^{1,5}$]undecanes via the stereospecific creation of a spiro carbon atom adjacent to an existing stereogenic quaternary carbon atom. It is worth mentioning that in the present radical cyclization reaction, a *trans*-hydrindane moiety was created in a stereospecific manner.[13,14]

Experimental Section

Melting points are recorded in capillaries and are uncorrected. ^1H and ^{13}C chemical shifts (δ) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). Off-resonance multiplicities, when recorded, are given in parentheses. Acme's silica gel (100−200 mesh) was used for column chromatography. Dry benzene was obtained by distillation over sodium. Dry ether was obtained by washing with ferrous sulfate followed by distillation over sodium. CuI, NBS, $^nBu_3SnH$, $PdCl_2$ were obtained from Fluka and used as received: AIBN was recrystallized from methanol and stored in the dark.

(2*S*,3*R*,5*R*)- and (2*R*,3*R*,5*R*)-2-Allyl-5-isopropenyl-2,3-dimethylcyclohexanones (7). To a cold (−10 °C), magnetically stirred, solution of lithium dimethylcopper [prepared from cuprous iodide (1.9 g, 10 mmol) and methyllithium in ether (20 mmol, 26 mL of 0.765 M)] was added a solution of (*R*)-carvone (**6**, 1.0 g, 6.66 mmol) in dry ether (15 mL) over a period of 15 min. The reaction mixture was further stirred for 30 min at room temperature, and a mixture of allyl bromide (8.0 g, 66.6 mmol, 5.8 mL) and HMPA (1.43 g, 8 mmol, 1.4 mL) was added over 5 min. The reaction mixture was stirred for 24 h at room temperature, quenched with 25% aqueous ammonia solution, and extracted with ether (3 × 15 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column, using ethyl acetate−hexane (1:48) as eluent, furnished a 9:1 epimeric mixture of allyl product **7** (1.22 g, 89%) as pale yellow oil. A small amount of major product was separated for the spectral data. $[\alpha]^{24}_D$: +37 (*c* 1.2, $CHCl_3$). IR (neat): ν_{max} 1705, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.63 (1 H, t of dd, J = 17.5, 9.5 and 7.3 Hz), 5.07 (1 H, d, J = 17.5 Hz), 5.07 (1 H, d, J = 9.5 Hz), 4.79 (1 H, s), 4.72 (1 H, s), 2.3−2.7 (5 H, m), 1.9−2.2 (2 H, m), 1.6−1.7 (1 H, m), 1.75 (3 H, s), 1.0 (3 H, s), 0.91 (3 H, d, J = 7.2 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 215.6, 148.2, 134.3, 118.5, 110.9, 52.4, 43.5, 42.7, 41.1, 37.4, 33.4, 21.5, 19.6, 16.6. Mass: *m*/*z* 206 (M^+, 10%). HRMS Calcd for $C_{14}H_{22}O$ 206.1671, found 206.1679.

(2*S*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-(2-oxopropyl)-cyclohexanone (8). A suspension of palladium chloride (61 mg, 0.34 mmol) and cuprous chloride (500 mg, 5 mmol) in DMF (2.5 mL) and water (0.5 mL, 28.2 mmol) was magnetically stirred in an oxygen atmosphere, created via evacuative displacement of air using an oxygen balloon, for 1 h at room temperature. A solution of allyl compound **7** (1.03 g, 5 mmol) in 1 mL of DMF was then added, and the reaction mixture was stirred for 24 h at room temperature in the oxygen atmosphere. Aqueous HCl (3 N, 5 mL) was added to the reaction mixture, and it was extracted with ether (3 × 10 mL). The ether layer was washed with saturated aqueous sodium bicarbonate solution followed by brine and dried (Na_2SO_4). Evaporation of the solvent and careful chromatography of the residue on a silica gel column using ethyl acetate−hexane (1:20 to 1:10) as eluent, furnished the diketone **8** (775 mg, 70%) as a white solid, which was recrystallized from hexane. mp 53−54 °C. $[\alpha]^{23}_D$: +6.1 (*c* 1.14, $CHCl_3$). IR (nujol): ν_{max} 1710, 1700, 895 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 4.83 (1 H, s), 4.75 (1 H, s), 2.78 (2 H, brs), 2.56 (2 H, brs), 2.2−2.5 (1 H, m), 2.12 (3 H, s), 1.65−1.85 (3 H, m), 1.72 (3 H, s), 1.02 (3 H, s), 0.88 (3 H, d, J = 7.2 Hz. ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.8 (s), 205.5 (s), 146.3 (s), 109.6 (t), 49.4 (t), 49.1 (s), 41.1 (t), 39.5 (d), 34.4 (d), 31.7 (t), 30.2 (q), 20.0 (q), 17.8 (q), 14.4 (q). Anal. Calcd. for $C_{14}H_{22}O_2$ C, 75.63; H, 9.97. Found C, 75.74; H, 10.19.

(11) Rodriguez, J.; Dulcere, J.-P. *Synthesis* **1993**, 1177.

(12) Jaggi, F. J.; Buchs, P.; Ganter, C. *Helv. Chim. Acta* **1980**, *63*, 872.

(13) There are only a very few reports in the literature on the construction of *trans*-hydrindane moiety via radical cyclization reactions,[14] and in most of them, the cyclopentane moiety was created by starting from 1,2-*trans*-substituted cyclohexanes, unlike the present case where the ring junction stereochemistry is created in the radcial cyclization reaction.

(14) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 941 and 980. Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1986**, *27*, 641.

(1*S*,2*R*,4*R*)-4-Isopropenyl-1,2-dimethylbicyclo[4.3.0]non-6-en-8-one (5). To a solution of the diketone **8** (686 mg, 3.09 mmol) in 1 mL of methanol was added 10% aqueous potassium hydroxide (1.73 mL, 3.71 mmol), and the reaction mixture was refluxed for 3 h. The reaction mixture was cooled and extracted with ether (3 × 10 mL). The ether extract was washed with water followed by brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a small silica gel column, using ethyl acetate−hexane (1:6) as eluent, furnished the enone **5** (600 mg, 95%). $[\alpha]^{25}_D$: +44.2 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max} 1700, 888 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.8 (1 H, s), 4.73 (1 H, s), 4.84 (1 H, s), 2.5−3.1 (3 H, m), 2.2 (2 H, s), 1.5−1.8 (3 H, m), 1.7 (3H, s), 1.12 (3 H, s), 0.91 (3 H, d, J = 6.14 Hz). ^{13}C NMR (50.0 MHz, $CHCl_3$ + $CDCl_3$): δ 207.6, 187.3, 146.0, 127.4, 111.7, 50.6, 46.7, 40.5, 36.4, 31.4, 30.0, 22.5, 18.5, 16.6. Mass: *m*/*z* 204 (M^+, 5%). 2,4-DNP derivative: mp (EtOH) 134−6 °C dec. Anal. Calcd. for $C_{20}H_{24}N_4O_4$ C, 62.48; H, 6.29. Found C, 61.9; H, 6.41.

(1*S*,5*S*,6*R*,8*R*,9*S*)- and (1*S*,5*S*,6*R*,8*R*,9*R*)-9-Methoxy-5,6,9-trimethyltricyclo[6.2.1.0^{1,5}]undecan-3-ones (10 and 11). To a cold (−10 °C), magnetically stirred solution of the enone **5** (408 mg, 2 mmol) in a 3:2 mixture of dichlorometahne−methanol (6 mL) was added NBS (300 mg, 1.69 mmol), in small portions over a period of 20 min. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with 10% aqueous NaOH solution, water followed by brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate−hexane (1:2.5 to 1:1.5) as eluent, furnished the bromoenone **9** (1:1, 520 mg, 83%), which was found to decompose slowly on standing and used immediately in the next reaction. IR (neat): ν_{max} 1700 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, 1:1 mixture of epimers): δ 5.79 (1 H, brs), 3.46 and 3.42 (2 H, s), 3.14 and 3.11 (3 H, s), 2.9−1.5 (6 H, m), 2.2 (2 H, s), 1.28 and 1.21 (3 H, s), 1.08 (3 H, s), 0.905 (3 H, d, J = 7 Hz).

To a refluxing solution of the bromoenone **9** (400 mg, 1.27 mmol) in 37 mL of dry thiophene-free benzene were added a mixture of tributyltin hydride (0.37 mL) and a catalytic amount of AIBN in benzene (130 mL) over a period of 45 min. The reaction mixture was refluxed for a further period of 8 h and concentrated under reduced pressure. The residue was taken up in ether (25 mL), washed with 1% NH_4OH (2 × 10 mL) solution followed by brine, and dried (Na_2SO_4). Evaporation of the solvent and careful chromatography of the residue on a silica gel column using ethyl acetate−hexane (1:49 to 1:29) as eluent, furnished the cyclized products **10** (102 mg, 34%) and **11** (98 mg, 32.7%). For the tricyclic ketone **10**. $[\alpha]^{25}_D$: −139.9 (*c* 3.7, $CHCl_3$). IR (neat): ν_{max} 1740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.25 (3 H, s), 2.53 (1 H, $^1/_2$ AB q, J = 18.4 Hz), 2.2−1.2 (11 H, m), 1.33 (3 H, s), 0.922 (3 H, s), 0.81 (3 H, d, J = 6.7 Hz). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 218.5 (s), 83.1 (s), 51.6 (q), 50.1 (2 C, s and t), 48.5 (t), 47.9 (t), 45.4 (d), 45.2 (s), 34.6 (d), 34.2 (t), 32.3 (t), 26.0 (q), 17.5 (q), 17.1 (q). HRMS Calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1770. For the tricyclic ketone **11**: mp (hexanes) 70−72 °C. $[\alpha]^{25}_D$: −145.7 (*c* 3.13, $CHCl_3$). IR (neat): ν_{max} 1740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.25 (3 H, s), 2.57 (1 H, $^1/_2$ AB q, J = 18.5 Hz), 2.2−1.3 (11 H, m), 1.30 (3 H, s), 0.925 (3 H, s), 0.814 (3 H, d, J = 6.6 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) (SEFT): δ 218.3 (C), 84.2 (C), 50.9 (C), 49.1 (CH_3), 50.5 (CH_2), 48.9 (CH_2), 47.7 (CH_2), 44.7 (C), 43.4 (CH), 34.7 (CH), 33.2 (CH_2), 32.5 (CH_2), 17.5 (2 C, CH_3), 17.1 (CH_3). Anal. Calcd for $C_{15}H_{24}O_2$ C: 76.23; H: 10.24. Found C: 76.45, H: 10.56%.

Acknowledgment. We thank the U.G.C., New Delhi, for the award of research fellowship to T.J.R.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **5**, **7** (major isomer), and **10** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960423C