Site-Selective Rhodium(II) Acetate Mediated Intramolecular Metal-Carbene Insertions into C-H Bonds of Bicyclo[2.2.1]heptanes: Efficient Syntheses of (+)-Albene and (-)-β-Santalene†

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Treatment of α-diazo ketones **1a-d** and **2a-d** with catalytic amounts of rhodium(II) acetate led to selective carbene insertions into C-H bonds resulting in cyclopentane-annulated products in high yields. The highly selective insertion realized into the *exo*-methyl C-H bond of **1a** has been utilized in the syntheses of (+)-albene (8) and (-)-β-santalene (11).

Introduction

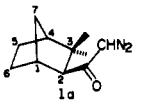
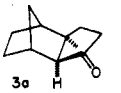
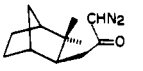
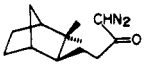
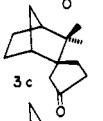
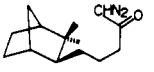
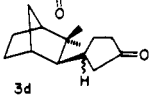
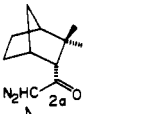
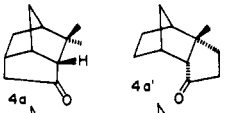
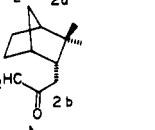
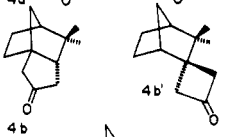
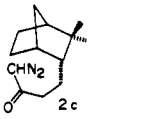
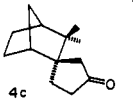
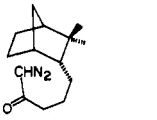
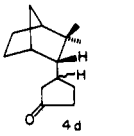
With the advent of rhodium(II) acetate[1,2] as a superior catalyst to generate transient electrophilic metal carbenes from α-diazo carbonyl compounds, intramolecular carbene insertion into unactivated C-H bonds has assumed strategic importance in C-C bond forming reactions in organic synthesis.[3] Lack of site selectivity,[4] however, appears to be a limitation in this approach. Recently, Taber[4b] et al. studied the $Rh_2(OAc)_4$-catalyzed intramolecular C-H insertion reactions of α-diazo-β-keto esters into freely rotating aliphatic side chains. This work was highly significant as the site selectivity of C-H insertion was probed on a conformationally mobile side chain rather than a constrained rigid system. The results not only showed that the formation of the five-membered ring was a favored process but also that C-H insertion into a more substituted carbon occurred faster than into a less substituted one for the same ring size. The latter observation was rationalized in terms of electronic effects. Although five-membered ring formation is commonly observed in conformationally mobile compounds, there are quite a few examples of C-H insertions leading to four- and six-membered rings depending upon the substrate.[3d] In this context, any strategy toward realizing a high order of site selectivity in C-H insertion reactions assumes importance. We wish to report herein that rigid carbon skeletons may dictate a high order of site selectivity in these reactions. The validity of this concept is demonstrated by cyclopentane annulation reactions[5] of bicyclo[2.2.1]heptane-derived α-diazo ketones of various tether lengths.

Results and Discussion

The substrates comprised the α-diazo ketones **1a-d** in the exo series and **2a-d** in the endo series (Table I), possessing the same tether lengths so that the comparative behavior of their metal-carbenes could be properly assessed. Diazo ketone **1a** was obtained in good yield, by the treatment of isocamphenilanic acid (**5**),[6] (*exo*-3,3-dimethylbicyclo[2.2.1]heptane-2-carboxylic acid), with oxalyl chloride followed by diazomethane. Photo-Wolff rearrangement[7] of **1a** led to the homologated acid which was converted to **1b**. By following the same protocol, **1c** and **1d** were obtained. Camphenilanic acid[6] (*endo*-3,3-dimethylbicyclo[2.2.1]heptane-2-carboxylic acid) similarly afforded the diazo ketones **2a-d**.

$Rh_2(OAc)_4$-Catalyzed C-H Insertion Reactions. Exposure of the diazo ketones to catalytic amounts of $Rh_2(OAc)_4$[4b] resulted in facile intramolecular metal-carbene insertions into C-H bonds leading to cyclopentane annulation. The products were characterized by their proton and ^{13}C NMR and IR spectral data as nor-

Table I. Product Distribution from Rhodium(II) Acetate Catalyzed Reactions of α-Diazo Ketones 1a-d and 2a-d

entry	substrate	product(s)	yield,[a] %
1.			85
2.			86
3.			78
4.			73
5.			4a, 60 4a', 25
6.			4b, 23 4b', 23
7.			88
8.			79

[a] Isolated yields after flash chromatography, based on the α-diazo ketone.

† NCL Communication No. 4823.

(1) For recent reviews, see: (a) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (c) Gerhard, M. *Top. Curr. Chem.* **1987**, *137*, 77.

(2) For use of other metal catalysts, see: (a) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361. (b) Wulfman, D. S.; Poling, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1980; Vol. 1, p 321.

(3) For representative recent synthetic applications see the following. (a) (-)-α-cuparenone: Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196. (b) (+)-Estrone; Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28. (c) (±)-Pentalenolactone: Taber, D. F.; Schuchardt, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 5289. (d) Cane, D. E.; Thomas, P. J. *Ibid.* **1984**, *106*, 5295.

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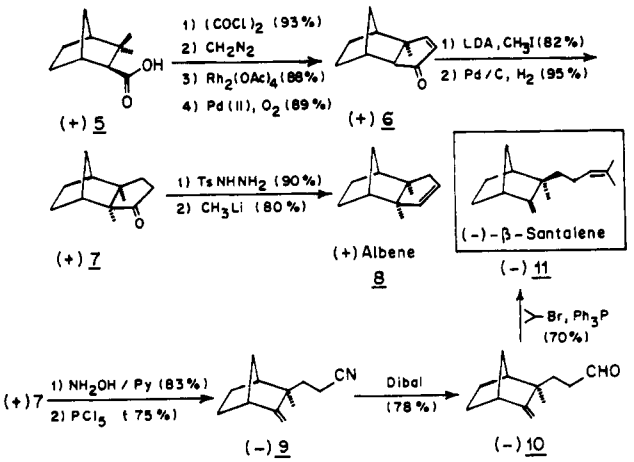
bornane-derived tricyclic ketones (Table I, **3a–d**, **4a–d**). Palladium(II) oxidations[8] of these ketones into the corresponding enones provided additional support for the structural assignments.

A cursory look at the table reveals that the intramolecular carbene insertion into C–H bonds has occurred in an efficient and selective manner (yields ranging between 73 and 88%) and the formation of the five-membered ring has been the exclusive phenomenon with a single exception of the endo ketone **2b** (entry 6) which furnished the spirobutanone **4b'**.

An analysis of the results in terms of the nature of the C–H bonds (primary, secondary, and tertiary) into which carbene insertion has occurred brings forth interesting information. At this point, it may be mentioned that intramolecular carbene insertions in rigid carbocyclic systems do not appear to have been reported so far. Even in acyclic systems, in context of the selectivity order referred to earlier,[4b] the observed occurrence of facile insertion into the methyl C–H bond (**1a** → **3a**, 85%) indicates that the electronic factors supposed to be governing regioselectivity in acyclic systems are not important here. Probably, the favorable geometrical disposition of the carbenoid center and the primary C–H bond may be responsible for the observed result. However, interestingly enough, Doyle[9] et al. have observed a selective carbenoid insertion into the methyl C–H bond in α-diazo esters; a similar selective carbene insertion noted by Adams[10] and co-workers has been attributed to the activation of the adjacent C–H bond by an oxygen heteroatom. The selectivity is also known to be influenced by the bridging ligand groups[11] on the metal. Notwithstanding these observations, selective carbene insertion into a methyl C–H bond under $Rh_2(OAc)_4$ catalysis in the absence of any heteroatom activation obtained in our study is noteworthy. Another interesting aspect of the present results is that selective carbene insertion has occurred even at the bridgehead carbon leading to carbon skeletons which are not easily accessible[12] (**1b** → **3b**, **2b** → **4b**). The basic skeletons of **3a**, **3b**, and **4b** are important as they are implicated in the rearrangement of tetrahydrodicyclopentadiene to adamantane.[13] It is interesting that the transformations of **1c** to **3c** and of **2c** to **4c** have not only resulted in spirocyclopentane annulation but have also served to juxtapose two quaternary centers.[14] When the tether length exceeds two (**1d**, **2d**), conformational control is lost and the substrates behave like their acyclic counterparts.

Scheme I



Besides enabling efficient cyclopentane annulation, the present methodology has the potential to generate enantiomerically pure tricyclic ketones as both Photo–Wolff[15] and carbene insertion reactions[3a] are stereospecific. We decided to capitalize on the efficient and highly selective carbene insertion into the C–H bond of the *exo*-methyl group in **1a** leading to **3a** in syntheses of important optically active natural products. Our efforts in this direction have culminated in the first total synthesis of the antipodal form of naturally occurring (–)-albene and a short synthesis of (–)-β-santalene (Scheme I).

(+)-Albene (8). The natural product (–)-albene, despite its isolation[16] as early as 1962 from the plant *Petasites albus* has engaged the attention of organic chemists for nearly three decades both for its structural elucidation[17] and synthesis.[18] Surprisingly, there has not been a single synthesis of this deceptively simple molecule in its optically active form.[19] The highly selective carbene insertion observed in the transformation of **1a** to **3a** prompted us to undertake the synthesis of optically active albene.

Treatment of diazo ketone (+)-**1a** (prepared from (+)-isocamphenilanic acid (**5**) with a catalytic amount of $Rh_2(OAc)_4$ furnished the enantiomerically pure ketone **3a** in a high yield. This ketone, possessing the tricyclic carbon skeleton and the exo orientation of the five-membered ring served as a key precursor to the target molecule. The only remaining tasks were the regio- and stereoselective introduction of a methyl group, deoxygenation, and a regiospecific placement of a carbon–carbon double bond. These functional group manipulations could be easily achieved as indicated in the scheme. Ketone (+)-**3a** on oxidation with $PdCl_2/Pd(OAc)_2/O_2$ was readily transformed into enone (+)-**6**, the methylation of which with lithium diisopropyl amide (LDA)/CH_3I followed by catalytic hydrogenation furnished the obvious and required penultimate intermediate (+)-**7** with right regio- and stereochemistry of the methyl group. Preparation of the tosylhydrazone of (+)-**7** and its decomposition[18c] with CH_3Li completed the synthesis of albene (**8**) in its optically active form in a 40% overall yield from (+)-**5**.

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(5) For recent reviews of cyclopentane annulation, see: (a) Ramaiah, M. *Synthesis* **1984**, 529. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.

(6) Buchbauer, G.; Haslinger, E.; Robien, W.; Vitek, R. *Monatsh. Chem.* **1983**, *114*, 113.

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(9) (a) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. E. *Tetrahedron Lett.* **1989**, 7001. (b) Doyle, M. P.; Shanklin, M. S.; Oon, S.; Pho, H. Q.; Van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384.

(10) Adams, J.; Poupart, M.; Grenier, L.; Schaller, C.; Ouimet, N.; Frennette, R. *Tetrahedron Lett.* **1989**, 1479.

(11) Callot, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, 4321.

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(13) de Mayo, P. In *Rearrangements in Ground and Excited States*; Academic Press: New York, 1980; pp 25–26.

(14) For a review, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(15) Wiberg, K. B.; Hutton, T. W. *J. Am. Chem. Soc.* **1956**, *78*, 1640.

(16) For isolation of (–)-albene, see: Hochmannova, J.; Novotny, L.; Herout, V. *Collect. Czech. Chem. Commun.* **1962**, *27*, 2711.

(17) For the structural elucidation, see: Baldwin, J. E.; Barden, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 6656.

(18) For racemic albene synthesis, see: (a) Baldwin, J. E.; Barden, C. *J. Org. Chem.* **1981**, *46*, 2442. (b) Trost, B. M.; Renant, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668. (c) Manzardo, G. G. G.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 627. (d) Chen, M.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 6558.

(19) For (–)-albene synthesis in 16% enantiomeric purity, see: Kreiser, W.; Janitschke, L. *Chem. Ber.* **1979**, *112*, 408.

(−)-β-Santalene (11). Being an important fragrant component of highly prized East Indian sandalwood oil, β-santalene has been a frequent target of synthetic efforts. Although there are many reported syntheses of the racemic[20] material, syntheses of its optically active form[21] are few. An examination of the optically active intermediate (+)-**7** which led to the synthesis of (+)-albene revealed that it is inherently suitable as a key precursor to optically active β-santalene. It was readily oximated, and the oxime derivative was subjected to Beckman fragmentation.[22] The resulting nitrile (−)-**9** on treatment with diisobutylaluminium hydride furnished the corresponding aldehyde (−)-**10**, the Wittig olefination of which completed the synthesis of optically active (−)-β-santalene (**11**) in a 20% overall yield from (+)-**5**.

It is interesting to note that the enone precursor of (+)-**7** on epoxidation with alkaline H_2O_2 can lead to a single epoxide which under Wharton[21d] reaction conditions results in an allylic alcohol; this alcohol under Swern oxidation conditions leads to an enone with inversion of chirality.[21d] Thus, the enone precursor of (+)-**7** has the inherent potential to lead to the syntheses of both (−)-albene and (+)-β-santalene, as well.

Summary

The present work clearly demonstrates that conformationaly rigid carbon frameworks can be advantageously utilized to achieve C–C bond formation by highly selective metal–carbene C–H insertion. This facet of carbene chemistry has been exemplified by the first total synthesis of optically active (+)-albene. Synthesis of (−)-β-santalene constitutes another example of natural product synthesis utilizing carbenoid intermediates.

Experimental Section

General Remarks. Solvents were purified by standard methods. $Rh_2(OAc)_4$ was prepared[23] from rhodium trichloride. $PdCl_2$ and $Pd(OAc)_2$ were purchased from Aldrich Chemical Co.

Usual workup means extraction of the reaction mixture in a suitable organic solvent (3 × 50 mL) (solvent is specified in the individual experiments), washing the organic layer with water and brine, drying(Na_2SO_4), concentration of the organic layer, subjecting the residue to flash column chromatography on silica gel (ethyl acetate-petroleum ether), and bulb-to-bulb distillation of the product under reduced pressure. The boiling points refer to oil bath temperatures.

^1H NMR and ^{13}C NMR spectra were recorded on 80-, 90-, or 300-MHz instruments. Only significant absorptions from the IR spectra are listed.

Preparation of Starting Materials. The substrates were prepared from camphenilanic acid, which in turn was prepared from camphene.[24] Camphenilanic acid was epimerized[25] to isocamphenilanic acid. Homologations of camphenilanic acid and isocamphenilanic acid (see below) provided the other acids in the endo and exo series, respectively. (+)-Isocamphenilanic acid (**5**) was prepared by resolution[26] of the racemate with (+)-dehydroabietylamine.

General Procedure for the Preparation of α-Diazo Ketones (1a–d, 2a–d, and (+)-1a). Oxalyl chloride (60 mmol) was added at 0 °C to a solution of the acid (50 mmol) in 20 mL of hexane. The reaction mixture was allowed to warm to room temperature and then refluxed for 1–2 h. After removal of excess oxalyl chloride and solvent, the acid chloride was distilled under reduced pressure. The above procedure was followed for all acids except camphenilanic acid, in which case, the reaction mixture, after addition of oxalyl chloride was stirred at room temperature for 4 h and concentrated in vacuo; the acid chloride was used as such without further purification. The yields of acid chlorides were 85–95%.

The acid chloride (25 mmol) was added at 0 °C, under nitrogen, to an ethereal solution of diazomethane[27] (75 mmol). After the solution was stirred for 1 h at 0 °C, the cooling bath was removed and stirring was continued for 4–6 h. The reaction mixture was concentrated, and the residue was flash chromatographed (silica, petroleum ether–ether) to yield the α-diazo ketone as a pale yellow oil in practically quantitative yield. This material, which was found to be homogeneous both by thin-layer chromatography (5% ethyl acetate in petroleum ether) and ^1H NMR spectroscopy, was used as such in further cyclization reactions.

1a: IR 2100, 1660 cm^{-1}; ^1H NMR 0.97 (s, 3 H), 1.15 (s, 3 H), 1.1–2.03 (m, 7 H), 2.12–2.46 (m, 2 H), 5.06 (s, 1 H).

1b: IR 2105, 1645 cm^{-1}; ^1H NMR 0.85 (s, 3 H), 1.02 (s, 3 H), 1.1–1.76 (m, 8 H), 1.83–2.37 (m, 3 H), 5.12 (s, 1 H).

1c: IR 2100, 1650 cm^{-1}; ^1H NMR 0.88 (s, 3 H), 0.96 (s, 3 H), 1.05–1.9 (m, 10 H), 2.1–2.4 (m, 3 H), 5.16 (s, 3 H).

1d: IR 2105, 1645 cm^{-1}; ^1H NMR 0.84 (s, 3 H), 0.93 (s, 3 H), 1.0–1.9 (m, 12 H), 2.0–2.4 (m, 3 H), 5.15 (s, 1 H).

2a: IR 2100, 1640 cm^{-1}; ^1H NMR 1.01 (s, 3 H), 1.1 (s, 3 H), 1.23–1.87 (m, 7 H), 2.0–2.47 (m, 2 H), 4.97 (s, 1 H).

2b: IR 2105, 1645 cm^{-1}; ^1H NMR 0.8 (s, 3 H), 1.0 (s, 3 H), 1.05–1.83 (m, 8 H), 1.93–2.4 (m, 3 H), 5.18 (s, 1 H).

2c: IR 2100, 1650 cm^{-1}; ^1H NMR 0.83 (s, 3 H), 0.95 (s, 3 H), 1.13–1.77 (m, 10 H), 1.95–2.4 (m, 3 H), 5.13 (s, 1 H).

2d: IR 2105, 1650 cm^{-1}; ^1H NMR 0.85 (s, 3 H), 0.94 (s, 3 H), 1.1–1.85 (m, 12 H), 2.0–2.4 (m, 3 H), 5.15 (s, 1 H).

***endo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-carboxylic acid (camphenilanic acid)**:[24] mp 92 °C; IR 3500–2500, 1715 cm^{-1}; ^1H NMR 1.04 (s, 3 H), 1.11 (s, 3 H), 1.2–2.0 (m, 8 H), 2.38 (m, 2 H), 9.5 (br s, 1 H); mass spectrum, *m/z* 168, 153, 125, 108, 101, 93, 87, 83, 67. For ^1H and ^{13}C NMR spectral data see ref 6.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.58; H, 9.44.

***exo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-carboxylic acid (isocamphenilanic acid)**:[25] mp 118 °C; IR 3400–2400, 1710 cm^{-1}; ^1H NMR 1.01 (s, 3 H), 1.16 (s, 3 H), 1.21–1.64 (m, 6 H), 1.77 (m, 1 H), 2.0 (m, 2 H), 2.40 (m, 1 H), 8.9 (br s, 1 H); mass spectrum, *m/z* 168, 153, 125, 108, 101, 93, 83, 67. For ^1H and ^{13}C NMR and mass spectral data see ref 6.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.22; H, 9.37.

General Procedure for Homologation of Acids. A solution of α-diazo ketone (50 mmol) in 300 mL of 10% aqueous dioxane (freshly distilled) was irradiated with a 200-W Hanovia lamp (Pyrex filter), under nitrogen, in a classical immersion well photo-assembly for 12–16 h. Dioxane was distilled off under reduced pressure, and the residue was taken up in ether and extracted with 5% NaOH. Acidification with 20% H_2SO_4 followed by a standard extractive workup with ether afforded the required homologated acid. The acids were characterized by their IR and ^1H NMR spectra and were used to prepare the diazo ketones.

***endo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-acetic acid**: yield 7.74 g (85%); mp 74 °C; IR 3400–2400, 1710 cm^{-1}; ^1H NMR 0.80 (s, 3 H), 0.99 (s, 3 H), 1.01–2.0 (m, 8 H), 2.1–2.44 (m, 3 H), 9.5 (br s, 1 H); ^{13}C NMR 20.43 (t), 21.50 (q), 24.52 (t), 31.90 (q), 32.24 (t), 36.99 (t), 37.07 (s), 42.05 (d), 46.34 (d), 49.03 (d), 180.7 (s);

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mass spectrum, *m/z* 182, 167, 139, 122, 107, 93, 83, 79, 67. For IR, ^{1}H NMR, and mass spectral data see ref 28.

***exo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-acetic acid**: yield 7.37 g (81%); mp 71 °C; IR 3400–2400, 1720 cm^{-1}; ^{1}H NMR 0.88 (s, 3 H), 1.02 (s, 3 H), 1.1–1.75 (m, 8 H), 1.85–2.45 (m, 3 H), 9.5 (br s, 1 H); ^{13}C NMR 24.07 (t), 25.03 (q), 27.61 (q), 29.49 (t), 35.62 (t), 36.20 (t), 40.31 (s), 43.84 (d), 49.41 (d), 49.77 (d), 180.66 (s); mass spectrum, *m/z* 182, 167, 139, 122, 113, 109, 97, 93, 91.

***endo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-propanoic acid**: yield 8.13 g (83%); mp 65 °C; IR 3500–2500, 1720 cm^{-1}; ^{1}H NMR 0.82 (s, 3 H), 0.94 (s, 3 H), 1.15–1.75 (m, 10 H), 2.0–2.4 (m, 3 H), 8.3 (br s, 1 H); mass spectrum, *m/z* 196, 181, 153, 135, 109, 93, 81, 69.

***exo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-propanoic acid**: yield 7.45 g (76%); mp 70 °C; IR 3400–2500, 1715 cm^{-1}; ^{1}H NMR 0.88 (s, 3 H), 0.98 (s, 3 H), 1.02–2.1 (m, 10 H), 2.15–2.49 (m, 3 H), 9.1 (br s, 1 H); mass spectrum, *m/z* 196, 181, 153, 135, 109, 93, 81, 67. For IR, NMR, and mass spectral data see ref 29.

***endo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-butanoic acid**: yield 7.86 g (75%); mp 64–66 °C; IR 3400–2400, 1720 cm^{-1}; ^{1}H NMR 0.80 (s, 3 H), 0.96 (s, 3 H), 1.1–1.9 (m, 12 H), 2.0–2.45 (m, 3 H), 9.5 (br s, 1 H); mass spectrum, *m/z* 210, 195, 167, 153, 149, 133, 109, 93, 81, 67.

***exo*-3,3-Dimethylbicyclo[2.2.1]heptane-2-butanoic acid**: yield 8.61 g (82%); mp 62–63 °C; IR 3500–2450, 1715 cm^{-1}; ^{1}H NMR 0.88 (s, 3 H), 0.98 (s, 3 H), 1.0–2.0 (m, 12 H), 2.0–2.4 (m, 3 H), 9.4 (br s, 1 H); mass spectrum, *m/z* 210, 195, 167, 153, 149, 131, 123, 109, 93, 81, 67.

General Procedure for $Rh_2(OAc)_4$-Catalyzed Cyclizations of α-Diazo Ketones. A solution of the α-diazo ketone (10 mmol) in 20 mL of CH_2Cl_2 was added under nitrogen over a period of 1 h to a suspension of 2 mg of $Rh_2(OAc)_4$ (catalyst to substrate ratio (molar equiv, 1:2200) in 80 mL of CH_2Cl_2. After being stirred for 12 h, the reaction mixture was filtered through a short column of silica gel, and the filtrate was concentrated and distilled under reduced pressure. The product was further purified by flash column chromatography (5% ethyl acetate in petroleum ether) and distilled under reduced pressure.

General Procedure for the Preparation of Enones from the Ketones 3a–c and 4a–c. A stirred mixture of ketone (2 mmol), 488 mg (2.74 mmol) of $PdCl_2$, and 488 mg (2.18 mmol) of $Pd(OAc)_2$ in 10 mL of 40% aqueous dioxane was heated at 90–95 °C under an atmosphere of oxygen for 12–14 h. Dilution of the reaction mixture with water, repeated extraction with petroleum ether, and usual workup yielded the enone.

3a: bp (bath temperature) 125 °C (4 mm); yield 1.390 g (85%); IR 1740 cm^{-1}; ^{1}H NMR 1.17 (s, 3 H), 1.1–1.9 (m, 9 H), 2.0–2.45 (m, 4 H); ^{13}C NMR 22.89 (t), 24.23 (q), 27.36 (t), 33.50 (t), 36.50 (t), 37.66 (t), 40.80 (d), 44.80 (s), 47.88 (d), 62.45 (d), 220.70 (s); mass spectrum, *m/z* 164, 149, 147, 134, 118, 104.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44, H, 9.83. Found: C, 80.11; H, 9.63.

Enone from 3a: bp (bath temperature) 118 °C (1 mm); yield 0.288 g (89%); IR 1703 cm^{-1}; ^{1}H NMR 1.18 (s, 3 H), 6.14 (d, *J* = 6 Hz, 1 H), 7.32 (d, *J* = 6 Hz, 1 H); ^{13}C NMR 19.60 (q), 23.51 (t), 27.66 (t), 34.06 (t), 40.29 (d), 41.90 (d), 51.80 (s), 60.52 (d), 134.41 (d), 170.66 (d), 211.89 (s); mass spectrum, *m/z* 162, 147, 154, 110, 96, 91.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.23; H, 8.87.

3b: bp (bath temperature) 135 °C (3 mm); yield 1.530 g (86%); IR 1740 cm^{-1}; ^{1}H NMR 0.92 (s, 3 H), 1.08 (s, 3 H), 1.22–1.89 (m, 8 H), 2.08–2.30 (m, 4 H); ^{13}C NMR 23.53 (t), 24.94 (q), 26.65 (q), 31.54 (t), 39.06 (s), 39.14 (t), 39.60 (t), 42.56 (t), 48.56 (d), 52.06 (s), 54.30 (d), 217.53 (s); mass spectrum, *m/z* 178, 164, 149, 136, 121, 107.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.79; H, 10.38.

Enone from 3b: bp (bath temperature) 125 °C (2 mm); yield 0.267 g (76%); IR 1705 cm^{-1}; ^{1}H NMR 1.14 (s, 3 H), 1.20 (s, 3 H), 1.4–2.0 (m, 7 H), 2.1 (br s, 1 H), 2.37 (m, 1 H), 5.62 (s, 1 H); ^{13}C NMR 23.62 (q), 24.52 (t), 28.02 (q), 31.08 (t), 40.37 (s), 41.06 (t), 41.88 (t), 49.67 (d), 56.64 (s), 118.23 (d), 202.37 (s), 210.78 (s); mass spectrum, *m/z* 176, 161, 148, 133, 119, 105, 91.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.56; H, 9.01.

3c: bp (bath temperature) 140 °C (5 mm); yield 1.499 g (78%); IR 1745 cm^{-1}; ^{1}H NMR 0.87 (s, 3 H), 1.01 (s, 3 H), 1.15–1.9 (m, 9 H), 2.02–2.44 (m, 5 H); ^{13}C NMR 23.48 (t), 23.56 (q), 24.34 (t), 26.46 (q), 31.62 (t), 34.74 (t), 37.21 (t), 40.05 (s), 45.04 (t), 45.76 (d), 50.20 (d), 51.58 (s), 218.40 (s); mass spectrum, *m/z* 192, 177, 175, 164, 149, 135, 122.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.93; H, 10.30.

Enone from 3c: bp (bath temperature) 130 °C (3 mm); yield 0.269 g (71%); IR 1705 cm^{-1}; ^{1}H NMR 0.95 (s, 3 H), 2.36 (m, 2 H), 5.92 (d, *J* = 6 Hz, 1 H), 7.58 (d, *J* = 6 Hz, 1 H); ^{13}C NMR 24.08 (t), 24.66 (t), 26.02 (q), 28.19 (q), 34.55 (t), 41.65 (t), 41.97 (s), 49.18 (d), 49.63 (d), 57.42 (s), 129.96 (d), 171.43 (d), 210.24 (s); mass spectrum, *m/z* 190, 175, 162, 147, 133, 120, 107, 91.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.36; H, 9.41.

3d: (3:1 diastereomeric mixture) bp (bath temperature) 145 °C (4 mm); yield 1.511 g (73%); IR 1735 cm^{-1}; ^{1}H NMR 0.93 (s), 0.94 (s), 0.96 (s), 0.99 (s), 1.1–2.6 (m); ^{13}C NMR major component 23.34, 24.87, 27.87, 29.38, 30.21, 35.47, 37.66, 40.36, 40.78, 46.25, 49.63, 49.72, 61.65, 218.92; minor component 24.37, 24.60, 30.42, 30.81, 35.63, 37.70, 37.85, 38.15, 40.69, 40.99, 41.57, 44.61, 60.41, 218.41; mass spectrum (of mixture), *m/z* 206, 192, 163, 148, 143, 109.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.22; H, 10.85.

4a: bp (bath temperature) 120 °C (2 mm); yield 0.984 g (60%); IR 1745 cm^{-1}; ^{1}H NMR 0.92 (s, 3 H), 1.03 (s, 3 H), 1.1–2.55 (m, 10 H). ^{13}C NMR 21.91 (q), 30.53 (q), 33.77 (t), 34.55 (d), 36.82 (t), 43.26 (s), 44.61 (t), 45.98 (d), 48.30 (d), 59.98 (d), 221.90 (s); mass spectrum, *m/z* 164, 149, 147, 134, 118, 104, 91.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.66; H, 10.12.

4a′: bp (bath temperature) 125 °C (2 mm); yield 0.410 g (25%); IR 1740 cm^{-1}; ^{1}H NMR 1.18 (s, 3 H), 1.1–2.6 (m, 13 H); ^{13}C NMR 23.82 (t), 24.05 (t), 29.49 (t) 29.98 (q), 33.99 (t), 41.24 (d), 41.35 (t), 47.09 (s), 48.29 (d), 61.39 (d), 222.16 (s); mass spectrum, *m/z* 164, 149, 147, 134, 118, 104, 91.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.13; H, 9.53.

Enone from 4a′: bp (bath temperature) 130 °C (3 mm); yield 0.252 g (78%); IR 1700 cm^{-1}; ^{1}H NMR 1.2 (s, 3 H), 2.14 (m, 2 H), 2.6 (br s, 1 H), 5.87 (d, *J* = 6 Hz, 1 H), 7.42 (d, *J* = 6 Hz, 1 H); ^{13}C NMR 23.59 (t), 24.68 (q), 26.04 (t), 40.19 (t), 41.12 (d), 44.68 (d), 54.82 (s), 60.20 (d), 131.84 (d), 170.89 (d), 212.14 (s); mass spectrum, *m/z* 162, 147, 134, 119, 105, 91.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.29; H, 8.51.

4b: bp (bath temperature) 128 °C (2 mm); yield 0.377 g (23%); IR 1735 cm^{-1}; ^{1}H NMR 0.92 (s, 3 H), 1.03 (s, 3 H), 1.15–2.65 (m, 12 H). ^{13}C NMR 21.95 (q), 30.58 (q), 33.85 (t) 34.63 (t), 36.68 (t), 43.33 (s), 44.68 (t), 46.06 (t), 48.13 (s), 48.40 (d), 60.08 (d), 187.61 (s); mass spectrum, *m/z* 178, 164, 149, 136, 121, 107.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.99; H, 10.34.

Enone from 4b. The product is identical with the enone obtained from **3b**.

4b′: bp (bath temperature) 116 °C (1 mm); yield 0.374 g (23%); IR 1785 cm^{-1}; ^{1}H NMR 0.94 (s, 3 H), 0.99 (s, 3 H), 1.1–2.6 (m, 12 H). ^{13}C NMR 23.36 (q), 24.60 (t), 24.94 (t) 28.16 (q), 34.70 (t), 38.34 (d), 43.97 (s), 49.21 (d), 49.21 (t), 49.73 (s), 54.64 (t), 207.25 (s); mass spectrum, *m/z* 178, 163, 150, 135, 121, 107, 105, 94.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.59; H, 9.89.

4c: bp (bath temperature) 141 °C (5 mm); yield 1.690 g (88%); IR 1745 cm^{-1}; ^{1}H NMR 0.89 (s, 3 H), 0.91 (s, 3 H), 1.15–2.7 (m, 14 H); ^{13}C NMR 22.38 (t), 22.63 (q), 23.85 (t) 27.09 (t), 27.69 (q), 34.63 (t), 36.99 (t), 39.60 (s), 46.08 (d), 49.56 (t), 49.89 (d) 51.50 (s), 218.38 (s); mass spectrum, *m/z* 192, 175, 164, 149, 135, 122, 91.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.42; H, 10.22.

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Enone from 4c: bp (bath temperature) 135 °C (2 mm); yield 0.262 g (69%); IR 1705 cm^{-1}; ^1H NMR 1.00 (s, 3 H), 2.55 (m, 2 H), 6.02 (d, J = 6 Hz, 1 H), 7.76 (d, J = 6 Hz, 1 H); ^{13}C NMR 23.44 (t), 23.84 (q), 24.51 (t), 29.52 (q), 37.31 (t), 43.69 (s), 47.05 (t), 49.70 (d), 53.07 (d), 57.09 (s), 132.75 (d), 169.91 (d), 210.15 (s); mass spectrum, m/z 190, 175, 162, 149, 133, 120, 91.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.13; H, 9.41.

4d (3:2 diastereomeric mixture): bp (bath temperature) 151 °C (3 mm); yield 1.627 g (79%); IR 1740 cm^{-1}; ^1H NMR 0.91 (s), 0.96 (s), 1.01 (s), 1.03 (s), 1.1–2.5 (m); ^{13}C NMR 20.15, 21.28, 21.41, 24.43, 27.93, 29.25, 29.45, 32.55, 34.98, 35.53, 36.77, 36.91, 37.77, 37.94, 38.29, 40.43, 40.75, 40.84, 44.84, 46.37, 49.45, 49.66, 49.76, 57.78, 61.72, 218.52, 219.28; mass spectrum, m/z 206, 192, 163, 148, 109, 91.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.15; H, 10.64.

Synthesis of (+)-Albene (8). (+)-Isocamphenilanic acid (*exo*-3,3-dimethylbicyclo[2.2.1]heptane-2-carboxylic acid (5)): prepared by resolution of the racemate with (+)-dehydroabietylamine;[26] mp 73–75 °C; $[\alpha]^{25}_D$ +17.4° (c 10, CH_3OH) [lit.[26] $[\alpha]^{28}_D$ +17.7° (c 10, CH_3OH)].

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.70.

(1*R*,2*S*,6*R*,7*S*)-6-Methyltricyclo[5.2.1.0^{2,6}]decan-3-one ((+)-3a): IR, ^1H NMR, and ^{13}C NMR data were the same as that of (±)-3a; $[\alpha]^{25}_D$ +34° (c 2.1 in $CHCl_3$).

6-Methyltricyclo[5.2.1.0^{2,6}]decen-3-one ((+)-6): IR, ^1H NMR, and ^{13}C NMR data were the same as that of the enone from (±)-3a; $[\alpha]^{25}_D$ +176.7° (c 1.8 in $CHCl_3$).

2,6-Dimethyltricyclo[5.2.1.0^{2,6}]decan-3-one ((+)-7). Enone (+)-6, 1.62 g (10 mmol), was added under nitrogen and at −78 °C to 10 mmol of lithium diisopropyl amide[30] in THF (10 mL). After the mixture was stirred for 30 min methyl iodide (1.56 g, 11 mmol) was added at −78 °C, and stirring was continued for 2 h. The temperature was slowly allowed to rise to 20 °C, and the reaction mixture was quenched with water and extracted with ether. Usual workup yielded the methylated product: 1.44 g (82%); mp 133–4 °C (lit.[18c] mp 130–131.5 °C); IR 1700, 1590 cm^{-1}; ^1H NMR 0.92 (s, 3 H), 1.02 (s, 3 H), 1.1–2.6 (m, 6 H), 6.24 (d, J = 5 Hz, 1 H), 7.29 (d, J = 5 Hz, 1 H); mass spectrum, m/z 176, 161, 148, 133, 122; for IR, ^1H NMR, and mass spectral data, see ref 18a; $[\alpha]^{25}_D$ +109.3° (c 0.451, $CHCl_3$).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.61; H, 9.30.

A solution of 1.32 g (7.5 mmol) of the above compound in 50 mL of C_2H_5OH was hydrogenated at room temperature and atmospheric pressure over 100 mg of 10% Pd/C. Filtration of reaction mixture over Celite and distillation under reduced pressure gave 1.27 g (95%) of (+)-7: mp 152–54 °C (lit.[31] mp 146–50 °C); IR 1730 cm^{-1}; ^1H NMR 0.88 (s, 3 H), 1.00 (s, 3 H), 1.1–2.45 (m, 12 H); mass spectrum, m/z 178, 163, 150, 135; For IR and ^1H NMR data, see ref 19; $[\alpha]^{25}_D$ +71.1° (c 1.66, $CHCl_3$).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.70; H, 10.31.

2,6-Dimethyltricyclo[5.2.1.0^{2,6}]decan-3-one Tosylhydrazone. A solution of 178 mg (1 mmol) of (+)-7 and 186 mg (1 mmol) of p-toluenesulfonyl hydrazide in 0.5 mL of ethanol containing one drop of concentrated HCl was refluxed for 2 h. The reaction mixture was cooled, and the solid that separated was filtered and recrystallized from 3 mL of CH_3OH: yield 311 mg (90%); mp 141–142 °C (lit.[18c] mp 138.5–140 °C); IR 3280, 3225, 1605 cm^{-1}; ^1H NMR 0.85 (s, 3 H), 0.88 (s, 3 H), 0.95–2.25 (m, 13 H), 2.39 (s, 3 H), 7.29 (d, 2 H), 7.8 (d, 2 H); mass spectrum, m/z 346, 278, 245, 190, 174, 133, 105; For IR and ^1H NMR data see ref 18c; $[\alpha]^{25}_D$ +47.2° (c 1.15, $CHCl_3$).

Anal. Calcd for $C_{19}H_{26}N_2O_2S$: C, 65.84; H, 7.857; N, 8.09. Found: C, 65.54; H, 7.80; N, 8.31.

(1*R*,2*R*,6*R*,7*S*)-2,6-Dimethyltricyclo[5.2.1.0^{2,6}]dec-3-ene ((+)-Albene, (+)-8). A solution of 138 mg (0.4 mmol) of the above tosylhydrazone in 2 mL of ether was treated dropwise with 0.7 mL (1 mmol) of a 1.4 M solution of methyllithium in ether at room temperature. After 45 min 3 mL of water was added, and the organic layer was separated. Extraction of the reaction mixture with ether followed by usual workup yielded 52 mg (80%) of (+)-albene (8): mp 112–114 °C (closed capillary) (lit.[31] mp 110–115 °C); IR 1630 cm^{-1}; ^1H NMR 0.94 (s, 6 H), 1.18–1.36 (m, 3 H) 1.49–1.67 (m, 3 H), 1.79 (m, 2 H), 2.22 (m, 2 H), 5.27 (dt, J = 2.5 and 6.5 Hz, 1 H), 5.57 (dt, J = 2.5 and 6.5 Hz, 1 H); ^{13}C NMR 17.99 (q), 20.56 (q), 23.70 (t), 23.70 (t), 34.08 (t) 46.47 (s), 46.95 (d) 50.20 (d), 51.68 (t), 56.24 (s), 128.19 (d), 139.49 (d) [from $CDCl_3$ 76.90]; mass spectrum, m/z 162, 147, 133, 121, 119; for ^1H NMR and ^{13}C NMR data see ref 32; $[\alpha]^{25}_D$ +31.4° (c 1.7, $CHCl_3$) [lit.[17b] $[\alpha]^{20}_D$ −33.9° ($CHCl_3$)].

Synthesis of (−)-β-Santalene ((−)-11). Dimethyltricyclo[5.2.1.0^{2,6}]decan-3-one Oxime. Ketone (+)-7 (890 mg, 5 mmol) and hydroxylamine hydrochloride (1 g, 14.3 mmol) were refluxed for 4 h in 10 mL of ethanol containing 2 mL of pyridine. The reaction mixture was diluted with water and extracted with ether. Standard workup followed by recrystallization from ether–petroleum ether yielded 801 mg (83%) of oxime: mp 110–112 °C (lit.[31] mp 108–111 °C); IR 3260, 1465 cm^{-1}; ^1H NMR 0.92 (s, 3 H), 0.99 (s, 3 H), 1.05–2.75 (m, 12 H), 8.2 (br s, 1 H); mass spectrum, m/z 193, 178, 175, 161, 148, 125, 108, 94; $[\alpha]^{25}_D$ +25.1° (c 1.325, $CHCl_3$).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.77; H, 9.71; N, 7.13.

3-(2-Methyl-3-methylenebicyclo[2.2.1]hept-2-yl)propanenitrile ((−)-9). The above oxime (580 mg, 3 mmol) was added slowly with stirring to a suspension of 600 mg of PCl_5 in 15 mL of petroleum ether over a period of 10 min. Stirring was continued for 1 h, after which the reaction mixture was quenched with water and extracted with ether. Usual workup gave 394 mg (75%) of the nitrile (−)-9: bp (bath temperature) 90–95 °C (1 mm); IR 2245 cm^{-1}; ^1H NMR 1.04 (s, 3 H), 1.1–2.8 (m, 12 H), 4.44 (s, 1 H), 4.79 (s, 1 H); mass spectrum, m/z 175, 160, 146, 132, 121, 105, 93; for IR, ^1H NMR, and mass spectral data, see ref 20h; $[\alpha]^{25}_D$ −66.2° (c 1.75, $CHCl_3$).

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.50; H, 9.87; N, 8.31.

3-(2-Methyl-3-methylenebicyclo[2.2.1]hept-2-yl)propanal ((−)-10). A solution of (300 mg, 1.7 mmol) of nitrile (−)-9 in 10 mL of toluene was cooled to −78 °C, and diisobutylaluminium hydride (1.9 mL, 1.9 mmol, 1 M solution in toluene) was added dropwise during 5 min. Stirring was continued at −78 °C for 1 h and then for 1 h at 0 °C. A mixture of ether and acetic acid was added, and stirring was continued for 1 h at 20 °C. The reaction mixture was extracted with petroleum ether, and usual workup gave 237 mg (78%) of the aldehyde (−)-10: bp (bath temperature) 100–105 °C (3–4 mm); IR 3070, 2715, 1730, 1660 cm^{-1}; ^1H NMR 1.0 (s, 3 H), 1.1–1.8 (m, 8 H), 1.98 (m, 1 H), 2.3–2.7 (m, 3 H), 4.46 (s, 1 H), 4.75 (s, 1 H), 9.76 (t, J = 1.5 Hz, 1 H); mass spectrum, m/z 178, 163, 160, 145, 132, 121; for IR, ^1H NMR, and mass spectral data, see ref 20h; $[\alpha]^{25}_D$ −82.5° (c 0.72, $CHCl_3$).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.03; H, 10.11.

(1*S*,2*R*,4*R*)-2-Methyl-2-(4-methyl-3-pentenyl)-3-methylenebicyclo[2.2.1]heptane ((−)-β-Santalene, (−)-11). To a solution of isopropyltriphenylphosphosphonium bromide[33] (1 mmol) in THF was added n-BuLi (1 mmol, 1.6 M in ether) at 0 °C. After being stirred for 15 min at 0 °C, the solution was cooled to −78 °C, and the aldehyde (−)-10 (0.85 mmol) in THF was added during 5 min. Stirring was continued for 1 h at −78 °C, after which the reaction mixture was quenched with water. Usual workup gave 100 mg (75%) of (−)-β-santalene (11): bp (bath temperature) 95–100 °C (2 mm); IR 3060, 2960, 2920, 2870, 2730, 1660, 1460, 1110, 880, 835 cm^{-1}; ^1H NMR 1.04 (s, 3 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 0.99–2.1 (m, 11 H), 2.63 (br d, J = 6.5 Hz, 1 H), 4.47 (s, 1 H), 4.70 (s, 1 H), 5.08 (br d, J = 6.5 Hz, 1 H); ^{13}C NMR 17.43 (q), 22.50 (q), 23.49 (t), 23.60 (t), 25.54 (q), 29.63 (t), 36.97 (t), 41.10 (t), 44.52 (d), 44.67 (s), 46.72 (d), 99.37 (t), 124.95 (d), 130.88 (s), 166.34 (s); mass spectrum, m/z 204, 189, 176, 161, 147, 133, 122, 94; for IR, ^1H NMR, and mass spectral data see ref 20h, for ^{13}C NMR data see ref 21c; $[\alpha]^{25}_D$ −103° (c 0.776, $CHCl_3$).

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Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.36; H, 11.75.

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Registry No. (±)-**1a**, 131131-42-5; (±)-**1b**, 131131-44-7; (±)-**1b** (acid precursor), 131131-59-4; (±)-**1c**, 131131-46-9; (±)-**1c** (acid precursor), 131131-61-8; (±)-**1d**, 131131-47-0; (±)-**1d** (acid precursor), 131131-63-0; (±)-**2a**, 131131-50-5; (±)-**2a** (acid precursor), 85506-67-8; (±)-**2b**, 131131-52-7; (±)-**2b** (acid precursor), 131131-58-3; (±)-**2c**, 131131-54-9; (±)-**2c** (acid precursor), 131131-60-7; (±)-**2d**, 131131-55-0; (±)-**2d** (acid precursor), 131131-62-9; (+)-**3a**, 131232-88-7; (±)-**3a**, 131131-43-6; (±)-**3b**, 131131-45-8; (±)-**3b** enone, 131131-64-1; (±)-**3c**, 131232-81-0; (±)-**3c** enone, 131131-65-2; (±)-**3d** (isomer 1), 131131-48-1; (±)-3d (isomer 2), 131131-49-2; (±)-**4a**, 131131-51-6; (±)-**4a′**, 131232-82-1; (±)-**4a′** enone, 131232-86-5; (±)-**4b**, 131232-83-2; (±)-**4b′**, 131131-53-8; (±)-4c, 131232-84-3; (±)-4c enone, 13232-87-6; (±)-4d (isomer 1), 131131-56-1; (±)-**4d** (isomer 2), 131131-57-2; (+)-**5**, 67518-96-1; (±)-**5**, 67519-00-0; (+)-**6**, 13232-77-4; (±)-**6**, 131232-85-4; (+)-**7**, 66701-34-6; (+)-7 enone, 131232-89-8; (+)-7 tosylhydrazone, 131232-90-1; (+)-7 oxime, 131232-91-2; (+)-**8**, 131232-78-5; (−)-**9**, 131232-79-6; (−)-**10**, 131232-80-9; (−)-**11**, 511-59-1.

Supplementary Material Available: NMR spectra of the homologated acids, (+)-albene and (−)-β-santalene and mass spectra of the homologated acids (17 pages). Ordering information is given on any current masthead page.

Sequential Radical Cyclization/Intermolecular Carbonyl Addition Reactions Initiated by Samarium(II) Iodide

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A sequential reductive coupling process promoted by samarium(II) iodide (SmI_2) is described. Thus, ethyl 2-acetyl-2-methyl-5-hexenoate, upon treatment with SmI_2 in the presence of a variety of aldehydes or ketones, undergoes an initial radical (ketyl) olefin cyclization. Subsequent reduction of the intermediate radical generated in this process produces a transient organosamarium species which can be trapped in situ by the added aldehyde or ketone electrophiles. Through this sequential radical cyclization/intermolecular carbonyl addition reaction, two new carbon–carbon bonds are generated in a one-pot process. Furthermore, a high degree of stereochemical control is established over three contiguous stereocenters, markedly increasing molecular complexity from the starting materials to the observed products.

Samarium(II) iodide (SmI_2) is an exceptional reagent for promoting intramolecular reductive cyclization reactions.[2] This reagent has been utilized in a variety of such processes, including ketone–olefin[3] and pinacolic coupling reactions.[3a] Intramolecular variants of these transformations proceed smoothly to provide densely functionalized carbocycles in many cases. In earlier studies, excellent stereoselectivity was achieved at up to three contiguous stereocenters,[3a] and products were generally obtained in good yields utilizing standard purification techniques.

The mechanism of the intramolecular ketone–olefin reductive coupling reaction was postulated to proceed via chelation-controlled ketyl addition to an unsaturated substituent, generating a cyclized radical intermediate.[3a] Intermolecular reduction of the cyclized radical intermediate by a second equivalent of SmI_2 led to formation of a transient organosamarium intermediate. The sequence was terminated by protonation of the organometallic utilizing an in situ proton source (MeOH or *t*-BuOH) (Scheme I, path A). Use of MeOD provided >95% deuterium incorporation at the methyl group in the final product and confirmed the existence of an intermediate organosamarium species.[3a] Based on the proposed mechanism, intermolecular entrapment of this organometallic with a variety of electrophiles was envisioned as a useful extension of the methodology (Scheme I, path B). The proposed sequential reaction process (radical cyclization/organometallic coupling) would place additional functionality in the cyclized products, thereby further in-

Table I. Sequential Radical Cyclization/Carbanion Carbonyl Addition Reactions Promoted by SmI_2 Utilizing Ethyl 2-Acetyl-2-methyl-5-hexenoate (1) as a Substrate

entry	carbonyl electrophile	product	% isolated yield[a]	diastereomeric ratio[b]
1	acetone	**2a**	79	31:1
2	3-pentanone	**2b**	73	65:1
3	diisopropyl ketone	**2c**	32	>200:1
4	cyclohexanone	**2d**	58	200:1
5	cyclopentanone	**2e**	65	60:1
6	2-methylcyclohexanone	**2f**	75	1:1
7	4-*tert*-butylcyclohexanone	**2g**	61	10:1
8	5-chloro-2-pentanone	**2h**	65	1:1
9	5-(diethylamino)-2-pentanone	**2i**	33	1:1
10	butanal	**2j**	55	17:17:1:1
11	isobutyraldehyde	**2k**	56	30:15:1:1
12	pivalaldehyde	**2l**	35	2:1
13	benzaldehyde	**2m**	0	–

[a] Refers to yields of purified material. All of these compounds have been fully characterized spectroscopically (^1H NMR, ^{13}C NMR, IR) and elemental composition has been established by high-resolution mass spectrometry and/or combustion analysis. [b] Determined on crude reaction mixture.

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