REGIO- AND STEREOSELECTIVE CONSTRUCTION OF VICINAL QUATERNARY CARBONS: TOTAL SYNTHESIS OF (±)-ALBENE

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Abstract—A regiospecific and stereoselective total synthesis of the trisnorsesquiternene (±)-albene, via a prochiral precursor is described. The ortho ester Claisen rearrangement of the allyl alcohol, obtained in two regiospecific reactions from a Diels-Alder adduct, followed by hydrolysis of the resultant ester furnished an ene acid in a highly stereoselective manner. Anhydrous copper sulphate catalysed intramolecular cyclopropanation reaction of the diazo ketone derived from the ene acid, generated a cyclopropyl ketone. The regiospecific reductive cleavage of this cyclopropyl ketone resulted in a prochiral ketone. Finally, Shapiro reaction on the tosylhydrazone, derived from the latter ketone, furnished (±)-albene.

INTRODUCTION

The optically active crystalline hydrocarbon albene (1), a trisnorsesquiterpene containing a unique exo-2,6-dimethyltricyclo[5.2.1.0^2,6]decane carbon framework incorporating two vicinal quaternary carbon atoms, was first isolated in 1962 by Novotny et al. [1] from the plant, Petasites albus. Later, it was found to be ubiquitous in species of the genera Petasites (white pestilence weed) and Adenostyles. This deceptively simple looking molecule has an interesting chemical history. The earliest structural studies carried out on albene showed it to be a tricyclic hydrocarbon with a disubstituted double bond in a five membered ring, for which Sorm et al. [2] proposed, provisionally the tetrahydrotriquinacene structure 2. In 1972 the tetrahydrotriquinacene structure was revoked [3] based on chemical degradation and correlation with camphene, and the endo structure 3 (now referred to as isoalbene) was assigned to albene. Later in 1978, the correct stereostructure of albene as exo-2,6-dimethyltricyclo[5.2.1.0^2,6]undec-3-ene (1) was established conclusively, largely due to the efforts of Kreiser and co-workers [4–6] via the total synthesis of the endo-isomer and reinterpretation of earlier results. Since the assignment of correct stereostructure to albene four research groups [7–10], Baldwin (1981), Trost (1982), Dreiding (1983) and Curran (1987) have reported the total synthesis of (±)-albene. In the authors’ laboratory a general methodology was developed [11] for the annulation of a cyclopentane ring with two vicinal quaternary carbon atoms starting from allyl alcohols based on ortho ester Claisen rearrangement [12] and diazo ketone cyclopropanation [13] reactions. The presence of two vicinal quaternary carbon atoms with methyl substituents prompted the extension of this methodology for the total synthesis of albene via the prochiral ketone 4. The retro synthetic analysis (Scheme 1) of albene (1) based on the ortho ester Claisen rearrangement and intramolecular diazo ketone cyclopropanation reactions readily identified the prochiral ketone 4, cyclopropyl ketone 5 and ene-acid 6 as the requisite precursors. The allyl alcohol 7 [14, 15] was chosen as the starting material in anticipation that the acetate side chain will be introduced from the exo face of the norborne moiety during the Claisen rearrangement which will result in the endo orientation for the tert-methyl group as required. The allyl alcohol 7...
was prepared in a straightforward manner starting from cyclopentadiene. Since the Diels–Alder reaction of cyclopentadiene with methyl tetrolate resulted in low yield of the adduct 8, Diels–Alder reaction was carried out using tetrolic acid. Thus reaction of cyclopentadiene and tetrolic acid in a sealed tube at 140° for 5 hr, followed by esterification of the adduct 9 with an excess of ethereal diazomethane furnished the ester 8 in 80% yield. The regiospecific hydrogenation of the less substituted olefin of the ester 8, using 10%-Pd/C as catalyst in ethyl acetate at atmospheric pressure of hydrogen, furnished the dihydro derivative, the ester 10. Since the reaction of the ester 10 with LAH was found to generate a mixture of allyl and saturated alcohols, it was reduced with diisobutylaluminium hydride (DIBAH) in toluene at -78° to furnish the allyl alcohol 7, the requisite starting material for the Claisen rearrangement, in 92% yield (Scheme 2).

The first quaternary carbon atom of albene was introduced using a highly stereoselective ortho ester Claisen rearrangement [14]. Thus, thermal activation of a solution of the allyl alcohol 7 and a catalytic amount of propionic acid in triethyl ortho-acetate for 48 hr at 180° generated the ene-ester 11 [16] in 81% yield, whose structure was delineated from its spectral data. The sterically preferred exo transition state 12 over the endo transition state 13 explains the exclusive formation of the exo product 11. The long reaction time required for this rearrangement was drastically reduced by employing a microwave oven [18]. Thus, microwave irradiation of a solution of the allylic alcohol 7, triethyl ortho-acetate and a catalytic amount of propionic acid in dry DMF in a clean Erlenmeyer flask for 14 min in a commercial microwave oven furnished the ester 11 in 87% yield. Hydrolysis of the ester 11 using 20% aqueous sodium hydroxide in methanol furnished the key intermediate of the sequence, the ene-acid 6, m.p. 85–87°, 76% yield.

The second quaternary carbon atom was created employing a copper catalysed intramolecular diazo ketone cyclopropanation reaction [15]. Reaction of the acid 6 with oxaly chloride in benzene at room temperature furnished the acid chloride 14 which on treatment with an excess of freshly prepared ethereal diazomethane at 0° generated the diazo ketone 15. Anhydrous copper sulphate catalysed decomposition of the diazo ketone 15 in refluxing cyclohexane, using a 100 W tungsten lamp for 5 hr, generated the cyclopropyl ketone 5 in 53% yield (from acid 6) via the intramolecular insertion of the resultant keto carbenoid into the exo-methylene whose structure rests secured from its spectral data (Scheme 3). The regiospecific formation of the cyclopropyl ketone 5 was a consequence of the insertion of the ketocarbene from the exo face of the molecule as it cannot approach from the other face of the double bond. This forces the cyclopropyl methylene to occupy the endo position, namely cis with respect to the endo tert-methyl group, thus creating the two quaternary centres in a highly stereoselective manner. The cyclopropyl ketone 5 was then transformed into the prochiral ketone 4, by the regiospecific cleavage of the C3-C4 bond of the cyclopropene ring. Thus, reduction of the cyclopropyl ketone 5 using lithium in liquid ammonia for 15 min at -33°, regiospecifically furnished the prochiral ketone 4 in 81% yield generating the second endo tert-methyl group. Both the 1H and 13C NMR (seven lines) spectra clearly revealed the presence of a plane of symmetry in the molecule. The regiospecificity in the cyclopropene ring cleavage can be readily explained [19] as it is well established that in the reduction of cyclopropyl ketones with lithium in liquid ammonia, of the two possibilities, the cyclopropene bond which is having maximum overlap with the p-orbital of the carbonyl system will be cleaved. Alternate to the reduction with lithium in liquid ammonia, catalytic hydrogenation (40 psi (≈ 276 kPa), H2-10% Pd/C; methanol, 5 hr) of the less substituted cyclopropene bond also transformed the cyclopropyl ketone 5 into the prochiral ketone 4 in quantitative yield.

The last phase in the synthesis, i.e. conversion of the ketone 4 into albene, requires the transformation of a cyclopentanone to a cyclopentene. For this purpose, a Shapiro reaction [20, 21] on the corresponding tosylhydrazone was adopted. Thus, treatment of the ketone 4 with tosylhydrazide in refluxing ethanol for four hours formed the tosylhydrazine 16, m.p. 162°, in 86% yield. Finally, treatment of the tosylhydrazine 16 in N,N,N',N'-tetramethylethylendiamine (TMEDA) and ether with an excess of n-butyllithium furnished (±)-albene ([1], m.p. 110–115° (lit. [1] 110–115°) in 65% yield. The 1H and 13C NMR spectra of our synthetic albene were found to be identical with those reported [5] in the literature for the natural product.
In conclusion, a stereoselective and regiospecific total synthesis of (+)-albene (1) was achieved via the prochiral ketone 4 using the ortho ester Claisen rearrangement and intramolecular diazoketone cyclopropanation reaction as key steps for the construction of the two vicinal quaternary carbons. It is evident from the foregoing discussion that if a methodology is available for the conversion of a prochiral cycloalkanone to a chiral cycloalkene, the ketone 4 can serve as a precursor to chiral albene. Recent reports on the conversion of prochiral ketones to chiral alkenes employing chiral amides [22] either for elimination [23] (equation 1) or generation of chiral enolates [24] (equation 2), enhanced the significance of the present synthesis, as a potential route to chiral albene.

EXPERIMENTAL

Melting points are not corrected. The chemical shifts (δ ppm) and coupling constants (Hz) in 1H (60 and 90 MHz) and 13C NMR (22.5 MHz) spectra are reported with reference to either internal tetramethylsilane (for 1H) or central line (77.1 ppm) of CDCl3 (for 13C). In the 13C NMR spectra off-resonance multiplicities, when recorded are given in parentheses. Low- and high-resolution mass measurements were carried out using a direct inlet mode. Relative intensities of the ions are given in parentheses. Elemental analyses were carried out using a Carlo Erba 1106 analyser. Acme’s silica gel (100–200 mesh) was used for column chromatography. Cyclopentadiene was freshly prepared by cracking dicyclopentadiene at 180°. Tetrolic acid and N-nitroso-N-methylurea were prepared according to the reported procedures [25].
hydrogen atmosphere (balloon) for 1.5 hr. The reaction mixture was then filtered through a small silica gel (5 g) column. Evaporation of the solvent furnished the deprotected ester 10 (6 g, 99%) as an oil. IR (neat): νmax cm⁻¹

1713 (C=O), 1632 (C=C), 1437, 1359, 1281, 1257, 1203, 1161, 1092, 1056. 1H NMR (60 MHz, CDCl₃): δ 6.61 (1H, s, O-CH₃), 3.15 (1H, br s, H-4), 2.75 (1H, br s, C-7), 2.16 (3H, s, olefinic CH₃).

13C NMR (22.5 MHz, CDCl₃): δ 165.8 (s, O-C=O), 160.0 (s, C-3), 131.8 (s, C-2), 50.4 (q, J = 20 Hz, olefinic CH₂), 46.6 (t, C-7), 44.9 (d, C-4), 45.9 (t, C-7), 43.1 (d, C-1), 26.2 (t) and 24.4 (t) (C-5 and 6), 14.4 (q, olefinic CH₃).

(3-Methylbicyclo[2.2.1]hept-2-en-2-yl)methyl ester (7). To a cold (-78°C) magnetically stirred solution of the ester 10 (5.5 g, 33 mmol) in dry toluene (25 ml) was added a solution of DIBAL-H (1.2M in toluene, 30 ml, 36 mmol) and the reaction was allowed to attain room temperature over a period of 1 hr. The reaction was then quenched with ether. The solids were filtered off and the residue was washed with ether (25 ml). The combined organic phase was dried (Na₂SO₄) and the solvent was evaporated. Purification of the residue over a silica gel (15 g) column using EtOAc–hexane (1:9) as eluent furnished the alcohol 7 (4 g, 92%) as an oil [17]. IR (neat): νmax cm⁻¹ 3340 (OH), 1692, 1446, 1278, 993. 1H NMR (90 MHz, CDCl₃): δ 4.21 and 4.00 (2H, ABq, J = 12.6 Hz, CH₂CO), 2.90 (1H, br s), 1.06 (6H, 2 × CH₃), 0.90–1.70 (6H, m–H, C-5 and 6). 13C NMR (22.5 MHz, CDCl₃): δ 140.0 (s, 0-C=O), 164.3 (s, C=CH₂), 101.3 (t, C=CH₂), 46.9 (d, C-1) and 45.0 (d) (C-4), 46.6 (t, C-7), 26.6 (t) and 25.3 (t) (C-5 and 6), 11.8 (q, CH₃). EIMS: m/z 138 (37%, M⁺). 121 (50), 110 (70), 95 (100), 91 (46).

Ethyl exo-(2-methyl-3-methylenebicyclo[2.2.1]hept-2-en-2-yl)acetate (11)

**Method A.** A solution of the allylic alcohol 7 (4 g, 28.9 mmol), triethyl orthoacetate (6 ml, 32.8 mmols) and a catalytic amount of propionic acid were taken in a Carius tube in N₂ and heated at 180° for 48 hr. The reaction mixture was cooled, diluted with ether (30 ml), washed with 0.5 M HCl followed by saturated NaHCO₃ solution and brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel (5 g) column using CH₂Cl₂ as eluant gave the acid 6 (2.75 g, 76%) which was recrystallized from hexane–CH₂Cl₂, m.p.: 85–87°C. IR (nujol): νmax cm⁻¹ 3000 (br, OH), 1707 (O=O), 1242, 935, 888 (C=CH₂). 1H NMR (90 MHz, CDCl₃): δ 4.83 (1H, s) and 4.41 (1H, s) (olefinic), 2.66 (1H, br s, H-4), 2.48 (1H, br s, H-1), 2.48 and 2.27 (2H, AB q, J = 16 Hz, CH₂–CO), 1.30–1.80 (6 H, m, H-5, 6 and 7), 1.2 (3H, s, tert-CH₃). 13C NMR (22.5 MHz, CDCl₃): δ 167.0 (s, O-C=O), 164.5 (s, C=CH₂), 101.3 (t, C=CH₂), 46.9 (d) and 45.0 (d) (C-1 and 4), 45.5 (t, C-7), 44.2 (s, C-2), 37.3 (t, CH₂COOH), 29.3 (t) and 23.7 (C-1 and C-4), 23.1 (q, tert-CH₃). (Found: C, 73.46; H, 9.08. C₁₁H₁₂O₂ requires C, 73.30; H, 8.95%).

7-Methyleneoctacyclo[6.2.1.0²⁴.0⁷₁₃]undecan-5-one (5)

1. Acid chloride (14). A solution of the acid 6 (2.5 g, 13.8 mmol) and oxalyl chloride (2 ml, 23.2 mmols) in dry benzene (5 ml) was magnetically stirred at room temperature for 2 hr. Evaporation of the solvent and excess oxalyl chloride under reduced pressure afforded the acid chloride 14 which was immediately used for the preparation of the diazo ketone.

2. Diazo ketone (15). A solution of the acid chloride 14, obtained above, in dry ether (10 ml) was added dropwise with stirring to a cold ethereal solution of diazomethane (excess, prepared from 15 g of N-nitroso-N-methyleurea and 50 ml of 50% aqueous KOH). The reaction mixture was stirred at room temperature for 2 hr, and the ether and excess diazomethane were removed by careful evaporation on a water bath. Filtration of the residue rapidly through a neutral alumina (8 g) column using EtOAc–hexane (1:20) as eluant furnished the diazo ketone 15 (2.2 g, 78%) as a viscous yellow oil. IR (neat): νmax cm⁻¹ 3075 (＝C–H), 2105 (diazo), 1635 (C=O), 1455, 1359, 1053, 880. 1H NMR (60 MHz, CDCl₃): δ 5.08 (1H, s, H=CH₂), 4.65 (1H, s) and 4.41 (1H, s) (olefinic), 2.66 (1H, br s, H-4), 2.50 (1H, br s, H-1), 2.05 and 2.35 (2H, AB q, J = 14 Hz, CH₂-C=O), 1.00–2.00 (6H, m, H-5, 6 and 7), 1.13 (3H, s, tert-CH₃).

3. Cyclopropyl ketone (5). A solution of the diazo ketone 15 obtained above was taken in dry cyclohexane
(25 ml) and added dropwise, over a period of 0.5 hr, to a refluxing (using a 100 W tungsten lamp placed at 2°
(1° ≈ 25.4 mm) from the reaction flask), magnetically
stirred suspension of anhydrous CuSO₄ (4.5 g) in cyco-
hexane (80 ml), and stirred at reflux for 5 hr. The reaction
mixture was cooled and the CuSO₄ was filtered off using
a sintered funnel. Evaporation of the solvent and puri-
fication of the residue on a silica gel (20 g) column using
EtOAc–hexane (1:2) as eluant furnished the tetracyclic
ketone 5 (1.12 g, 53% from acid 6) as a waxy, low melting
solid. IR (neat): νmax cm⁻¹ 1730 (C=O), 1470, 1296, 1236,
1161, 1061 cm⁻¹. 1H NMR (90 MHz, CDCl₃): δ2.24 and 2.02
(2H, AB 4, J = 18 Hz, CH₂-C=O), 2.16 (1H, br s, H-4),
1.20–2.00 (10 H, m), 0.98 (3 H, s, tert-CH₃), EIMS: m/z 176
(31%, M+). 13C NMR (22.5 MHz, CDCl₃): δ215.1 (s, C=O),
56.0 (t, CH₂CO), 50.8 (s, CH₂CO), 48.2 (d) and 42.0 (d)
(C-1 and 8), 40.5 (s, C-2), 37.7 (t, C-11), 35.2 (d, C-4),
25.0 (2C, t, C-9 and 10), 23.1 (q, C-7), 17.2 (q, C-3),
143.8, 135.7, 129.6 (2C) and 127.9 (2C) (aromatic), 50.5,
50.3 (2C), 49.0, 47.0, 44.9, 34.5, 23.6, 23.4, 21.7, 21.0
(2C).

(2) Shapiro reaction. To a magnetically stirred, cold
(0°C) solution of the tosylhydrazone 16 (800 mg, 2.3 mmol)
in dry ether (5 ml) and TMEDA (2.5 ml) was added a solution of n-butyl lithium (1.6 M in hexanes, 4 ml,
6.4 mmol). The reaction mixture was stirred for 6 hr at 0°C,
then quenched with wet ether, acidified with HCl (0.5 M)
and extracted with ether 3 × 10 ml. The ether extract was
washed with saturated aqueous NaHCO₃ and brine, and
dried (Na₂SO₄). Careful evaporation of the solvent fol-
lowed by purification of the residue on a silica gel (3 g)
column using pentane as eluant furnished (1) albene
(1, 245 mg, 65%) as a white solid which was sublimed
at 60°/50–60 mm. m.p.: 110–115°C (Lit. [1] 110–115°C).

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