Intramolecular Ketalization of Functionalized 7-Norbornenols

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Abstract: Convenient access to polycondensed heterocyclic networks has been realized through exposure of bridged hydroxy acetones to appropriate reagents.

Key words, photochemistry, heterocycles, acetals, sulfones, sulfoxides

We envisioned the synthesis of the oxygenated diterpene pseudolaric acid A (1), which was isolated from the root bark of Pseudolarix kaempferi Gordon (pinaceae), to originate via the properly substituted norbornenol (Scheme 1). The structural features inherent to 3 were expected to be obtained by photo-1,3-rearrangement of the bicyclic enone 4. Herein we report the synthesis of 3 and the subsequent formation of polycondensed heterocyclic networks encountered during attempts to form 2.

Scheme 1 Retrosynthetic analysis of pseudolaric acid A (1)

The synthetic approach commenced with the lithiation of vinylic bromide 5 in diethyl ether at low temperature, followed by 1,2-addition of this organometallic reagent to aldehyde 6 (Scheme 2). The resulting 1:1 diastereomeric mixture of allylic carbinols 7 and 8 was directly irradiated in the presence of the copper(I) triflate–benzene complex (5 mol% in Et₂O) as catalyst. A salient feature of the photocyclization that operates is the anticipated adoption of the thermodynamically more favored conformers 9 and 10 en route to the bicyclic products 11 and 12, respectively. The modest levels of competitive silyl deprotection that gave rise to 11b and 12b proved ideally suited to chromatographic separation and to the assignment of relative configuration to the diols by means of NOE correlations (see formulas in Scheme 2). Once this information was made known, separation of diastereomers at this stage was no longer warranted since sequential exposure to tert-butyldimethylsilyl triflate and 2,6-lutidine in advance of oxidation with 2-iodoxybenzoic acid (IBX) allowed for matched conversion to 13 in high yield. The required desaturation of 13 as in 4 proved to be highly problematic. After the evaluation of many varied reaction conditions, including a-halogenation/elimination, a-selenation/elimination, and 2-iodoxybenzoic acid oxidation, the use of stoichiometric levels of palladium(II) acetate in dimethyl sulfoxide at room temperature for two days emerged as the most workable option.

Upon ultraviolet irradiation, 4 was converted into the synthetically useful β,γ-unsaturated ketone 3 (25%, Scheme 3), which proved readily separable from the polymer inevitably formed under the best circumstances. The main strength of this transformation is that it results in the direct generation of a nonsymmetric 7-ketonorbornene, nucleophilic attack on which was expected to favor approach syn to the double bond to avoid the exo-hydrogens encountered via an anti approach. The first construct for the formation of 2 to be examined originated in the addition of the Grignard reagent derived from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane to the ketone 3. Installation of the new C–C bond arose from nucleophilic attack very predominantly from that direction syn to the olefinic functionality to deliver 16. The silyl ether so formed was cleaved efficiently with tetrabutylammonium fluoride to liberate diol 17. Treatment of 17 with pyridinium p-toluenesulphonate in acetone at room temperature, in order to afford a dicarbonyl compound for ring closure via a McMurry reaction, resulted in a dramatic increase in structural complexity as a direct result of alternative ketal formation with the loss of ethylene glycol. The new bonding arrangement resident in 18 holds interest when one considers that full retention of configuration is maintained at the original tertiary carbinol site. It is, of course, possible that ionization does not operate during the course of this transformation. However, should the incipient carbocation be generated, the powerful anchimeric assistance earlier recognized in simpler anti-7-norbornenyl
derivatives would be anticipated and lead comparably to 18. Although a mechanistic distinction was not pursued, the ultimate involvement of the primary hydroxy group led to incorporation of a fourth ring. The bonding arrangement held together in 18 can be considered to constitute a heterocyclic analogue of 2. Various attempts to open the acetal were unsuccessful.

An apparent strength of this chemistry is its generality. Thus, we have also achieved the conversion of 17 into bromide 19 as a prelude to admixture with an equivalent of thiourea (Scheme 4). Direct alkaline saponification of the isothiouronium salt so formed led to cyclization with
concomitant unexpected in situ oxidation to give the sulf oxide 20 in 50% overall yield. Although 20 proved to be a single diastereomer, no effort was made to decipher its configuration. Rather, 20 was oxidized with m-chloroperoxybenzoic acid in diethyl ether to generate sulfone 21, whose heightened crystallinity allowed the corroboration of structure by X-ray crystallography. Conversion of 21 into the corresponding thioalcohol and subsequent oxidation in order to perform a Ramberg–Bäcklund ring contraction to install the desired seven-membered ring was unsuccessful.14

In summary, we have uncovered the capability of 7-norbornenols of type 17 that carry a functionalized side chain linked to one of the bridgehead centers to undergo intramolecular ketalization with generation of highly condensed frameworks. The ready accessibility of substances such as 18, 20, and 21 is illustrative of a potentially general route for the production of related structures. Alternative methods for the construction of the seven-membered ring required for the preparation of pseudolactic acid A (1) are currently being investigated and will be reported in due course.

All reactions were performed under an atmosphere of dry N2 in oven- or flame-dried glassware. All other solvents and reagents were purified by standard techniques or used as supplied.15 Silica gel column chromatography (flash chromatography) was carried out using silica gel 60 (230–400 mesh).16 Brine refers to sat. aq NaCl soln. Melting points were measured on a capillary melting point apparatus and are uncorrected. IR spectra were recorded as evaporated films. All 1H and 13C NMR spectra were recorded on a Bruker Avance 400 MHz (operating frequencies: 1H, 400.00 MHz; 13C, 100.53 MHz) and 500 MHz (operating frequencies: 1H, 500.02 MHz; 13C, 125.73 MHz) FT spectrometers at r.t. using the NMR solvent as an internal reference. The reference values used for CDCl3 were δ = 7.26 and 77.00 for 1H and 13C NMR spectra, respectively. The mode of ionization for LR-MS and for HRMS was electrospray.

(4R,6S*)-1-[4-(tert-Butyldimethylsiloxyl)ethyl]-4,6-dimethyl-3-methyleneoct-7-en-4-ol (7) and (4R,6R*)-1-[4-(tert-Butyldimethylsiloxyl)ethyl]-4,6-dimethyl-3-methyleneoct-7-en-4-ol (8)

To a soln of 5 (19.50 g, 73.58 mmol) in Et2O (400 mL) at −78 °C was added 1.6 M n-BuLi in hexanes (105 mL, 168 mmol) and the resultant soln was allowed to warm to 0 °C over 1 h. A soln of 6 (9.50 g, 9.69 mmol) in Et2O (150 mL) was then added. After 4 h at 0 °C, H2O (150 mL) was added. The mixture was extracted with Et2O (3 × 100 mL), dried (anhyd Na2SO4), and concentrated in vacuo. Purification by flash chromatography (hexanes–Et2O, 3:1) afforded a inseparable mixture (1:1) of 7 and 8 as a colorless oil; yield: 18.53 g (80%); δR = 0.29 (hexanes–Et2O, 4:1).

IR (film): 3434 (br), 1646, 1472, 1256 cm–1.

1H NMR (400 MHz, CDCl3): δ = 0.06 (s, 3 H), 0.06 (s, 3 H), 0.87 (m, 12 H), 1.41 (m, 2 H), 1.64 (m, 1 H), 1.72 (m, 1 H), 1.80 (m, 1 H), 1.91 (m, 2 H), 2.14 (m, 3 H), 3.69 (m, 3 H), 4.05 (dd, dd = 11.0, 6.4 Hz, 1 H).

13C NMR (100 MHz, CDCl3): δ = –5.6, –5.5, 18.2, 19.0, 21.5, 22.4, 25.8, 37.4, 39.0, 42.8, 49.2, 50.9, 60.4, 77.1.

11b

Orange solid; yield: 102 mg (13%); mp 62–64 °C; δR = 0.49 (Et2O).

IR (film): 3355 (br), 1684, 1654, 1458 cm–1.

1H NMR (500 MHz, CDCl3): δ = 1.07 (d, J = 7.3 Hz, 3 H, Me), 1.40 (m, 1 H, Hb), 1.55 (m, 1 H, Hgt), 1.71 (m, 2 H, H7b and H3a), 1.87 (m, 2 H, CH2CH2OH and H4b), 2.02 (m, 1 H, H5b), 2.13 (m, 2 H, CH2CH2OH and H6b), 2.45 (m, 1 H, H3), 2.98 (br s, 2 H, OH), 3.66 (td, dd = 10.4, 2.3 Hz, 1 H, CH3CH(OH), 3.75 (m, 1 H, CH2CH2OH), 3.91 (d, dd = 5.2 Hz, 1 H, H2).

13C NMR (100 MHz, CDCl3): δ = 20.9, 22.7, 27.0, 37.1, 40.4, 41.5, 51.5, 52.9, 59.3, 80.2.

1H NMR (400 MHz, CDCl3): δ = 19.0, 21.5, 22.3, 37.3, 42.6, 48.9, 50.8, 59.5, 77.6.

HRMS: m/z [M + Na]+ calcd for C16H30NaO2Si: 305.1913; found: 305.1917.

(1R*,2S*,4R*,5S*)-1-[2-(2-tert-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]hept-3-en-2-one (2a) 1H NMR (400 MHz, CDCl3): δ = 0.06, (s, 6 H), 0.90 (s, 9 H), 1.24 (d, J = 7.1 Hz, 3 H), 1.82 (m, 3 H), 2.31 (m, 1 H), 2.48 (m, 1 H), 2.92 (dd, J = 10.1, 7.7 Hz, 1 H), 3.68 (m, 2 H).

13C NMR (100 MHz, CDCl3): δ = 5.4, 18.2, 21.3, 21.9, 25.9, 27.3, 34.6, 36.8, 45.1, 46.1, 51.3, 59.9, 223.0.


(1R*,4R*,5S*)-1-[2-(2-tert-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]hept-3-en-2-one (4) 1H NMR (400 MHz, CDCl3): δ = 0.06, (s, 3 H), 0.21 (s, 9 H), 0.90 (s, 9 H), 0.96 (d, J = 7.1 Hz, 3 H), 1.82 (m, 3 H), 2.06 (m, 3 H), 2.31 (m, 1 H), 2.48 (m, 1 H), 2.92 (dd, J = 10.1, 7.7 Hz, 1 H), 3.68 (m, 2 H).

13C NMR (100 MHz, CDCl3): δ = 5.4, 18.0, 21.4, 31.9, 25.9, 27.2, 34.4, 36.8, 45.4, 46.1, 51.3, 59.9, 223.0.


(1R*,2S*,4R*,5S*)-1-[2-(2-tert-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]hept-3-en-2-one (1a) 1H NMR (400 MHz, CDCl3): δ = 0.94 (s, 3 H), 0.90 (s, 9 H), 1.30 (s, 3 H), 1.45 (m, 1 H), 1.67 (m, 2 H), 1.69 (d, J = 1.3 Hz, 3 H), 1.80 (m, 1 H), 1.96 (m, 3 H), 2.09 (m, 1 H), 2.30 (d, J = 3.3 Hz, 1 H), 3.39 (br s, 1 H), 3.69 (m, 1 H), 3.78 (td, J = 10.7, 3.4 Hz, 1 H), 3.94 (m, 4 H), 4.00 (br s, 1 H), 5.28 (m, 1 H).

1C NMR (100 MHz, CDCl3): δ = 12.5, 23.5, 23.6, 24.6, 28.0, 31.1, 34.9, 52.7, 59.1, 59.3, 64.5, 64.6, 64.8, 69.8, 110.3, 132.5, 143.3.

(1R*,2S*,4R*,5S*)-1-[2-(2-tert-Butyldimethylsiloxy)ethyl]-3-methylbicyclo[2.2.1]hept-2-en-7-one (3) 1H NMR (400 MHz, CDCl3): δ = 1.96 (m, 3 H), 2.09 (m, 1 H), 2.30 (d, J = 3.3 Hz, 1 H), 3.39 (br s, 1 H), 3.69 (m, 1 H), 3.78 (td, J = 10.7, 3.4 Hz, 1 H), 3.94 (m, 4 H), 4.00 (br s, 1 H), 5.28 (m, 1 H).

(1R*,5R*)-5,10-Dimethyl-4,14-dioxatetracloro[7.2.2.15,8.01,8]tetradec-10-ene (18)
To a soln of 17 (11 mg, 0.041 mmol) in acetonitrile (2 mL) at r.t. was added PPTS (~1 mg) and the resultant mixture was stirred for 2 h. The mixture was washed with sat. NaHCO3 soln (3 × 10 mL), dried (anh Na2SO4), and concentrated in vacuo. Purification of the residue by flash chromatography (hexanes–Et2O, 4:1) afforded 18 as a colorless oil; yield: 7 mg (72%); Rf = 0.49 (hexanes–Et2O, 4:1).

HR (film): 1632, 1440, 1305, 1276 cm–1.

1H NMR (400 MHz, CDCl3): δ = 8.95 (td, J = 10.8, 3.6 Hz, 1 H), 1.03 (td, J = 11.2, 3.30 Hz, 1 H), 1.36 (s, 3 H), 1.52–1.76 (m, 3 H), 1.71 (d, J = 1.3 Hz, 3 H), 1.85 (m, 3 H), 2.01 (m, 2 H), 2.30 (d, J = 3.6 Hz, 1 H), 3.50 (dt, J = 12.5, 3.0 Hz, 1 H), 3.90 (t, J = 11.8 Hz, 1 H), 5.39 (m, 1 H).

13C NMR (100 MHz, CDCl3): δ = 16.3, 23.0, 23.1, 25.4, 27.0, 30.2, 30.3, 32.9, 43.3, 55.2, 55.9, 91.3, 101.3, 130.8, 144.6.

IR (film): 1654, 1458, 1438, 1379 cm–1.

A portion of this material was recrystalized (Et2O) for X-ray crystal structure analysis.

References


10. (R*,5R*)-5,10-Dimethyl-14-oxa-4,4-thiatetrayclo[7.2.2.15,8.01,8]tetradec-10-ene-4,4-dione (21)
To a soln of 20 (55 mg, 0.20 mmol) in EtOH (15 mL) at 0 °C was added MCPBA (53 mg, 0.31 mmol) and the resultant soln was allowed to warm to r.t. over 2 h. The mixture was washed with sat. NaHCO3 soln (3 × 10 mL), dried (anh Na2SO4), and concentrated in vacuo to afford 21 as a white solid; yield: 52 mg (94%); mp 109–111 °C; Rf = 0.50 (hexanes–Et2O, 19:1). A portion of this material was recrystalized (Et2O) for X-ray crystal structure analysis.

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of the relative stereochemistry at the newly formed stereogenic center was made on the basis of the \(^1\)H NMR chemical shifts of the signals corresponding to the vinyl and bridgehead protons (anti \(\delta = 5.29\)/syn \(\delta = 5.55\) and anti \(\delta = 2.29\)/syn \(\delta = 2.38\), respectively). See: Clark, F. R. S.; Warkentin, J. Can. J. Chem. 1971, 49, 2223.


(17) Signal disappeared upon the addition of a drop of D\(_2\)O to the NMR sample.