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Novel tandem ring-opening/ring-closing metathesis reactions of functionalized cyclohexenoids derived from (−)-α-pinene

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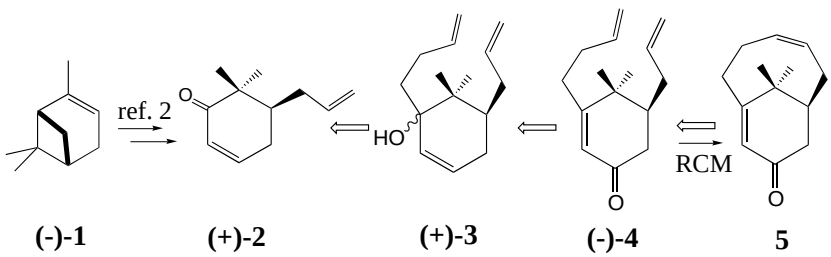
Abstract—The cyclohexenone (+)-**2**, readily obtained from (−)-α-pinene **1** was elaborated to (+)-**3** in an attempt to construct the AB rings of taxoids employing the ring-closure metathesis (RCM) reaction as the key step. In the event, a novel ring-opening/ring-closing metathesis reaction was encountered in the relatively strain free cyclohexenyl ring of (+)-**3**.

α-Pinene **1**, a monoterpene found abundantly in Nature has been extensively explored as a chiral building-block in many synthetic endeavors.[1] We have recently reported the restructuring of (−)-**1** into various interesting frameworks via the intermediacy of the readily available enone (+)-**2**, by employing intramolecular tandem Michael, aldol and [2+2]-photocycloaddition reactions.[2] As a part of our continuing interest in the utilization of (+)-**2** in natural product syntheses, we became interested in its elaboration to the AB rings of taxoids[3] as shown in the retrosynthetic sequence displayed in Scheme 1. The key final step in this approach was a ring-closure metathesis (RCM) reaction in either (+)-**3** or (−)-**4** to generate the bicyclo[5.3.1]undecane framework **5** of taxoids.[4] While executing our projected approach (Scheme 1) to the AB rings of taxoids, we have unexpectedly encountered a ring-opening/ring-closing metathesis sequence in the cyclohexenyl system. Normally, tandem ring-opening/ring-closing metathesis reactions are observed in strained rings where there is a tendency to undergo ring opening to release strain or in cycloalkene allyl ethers.[5,6] The tandem reactions reported herein are novel because they involve the relatively less strained cyclohexenyl ring undergoing ring opening, an event which has been reported scarcely in the literature.[5]

We have previously reported[2] a convenient synthesis of (+)-**2** from α-pinene **1** and in order to implement the projected theme of Scheme 1, a second olefin bearing side arm needed to be appended. For this purpose, a 4C butenyl chain was added via a Barbier reaction between (+)-**2** and butenyl bromide in the presence of lithium metal to yield (+)-**3** (Scheme 2). PCC oxidation in (+)-**3** furnished the desired transposed enone (−)-**4**.[2] A ring-closure metathesis reaction on **4** using Grubbs' catalyst $Ru[(PCy_3)_2Cl_2CHPh]$ was attempted with the expectation that the terminal olefins will react and afford the bicyclic skeleton **5**. However, even after several attempts no clean product formation was observed and the tlc and spectral scrutiny of the reaction mixture indicated the formation of a complex mixture of oligomers or polymers as a result of intermolecular metathesis. Attributing the failure of this reaction to



(-)-1 (+)-2 (+)-3 (-)-4 5

Scheme 1.

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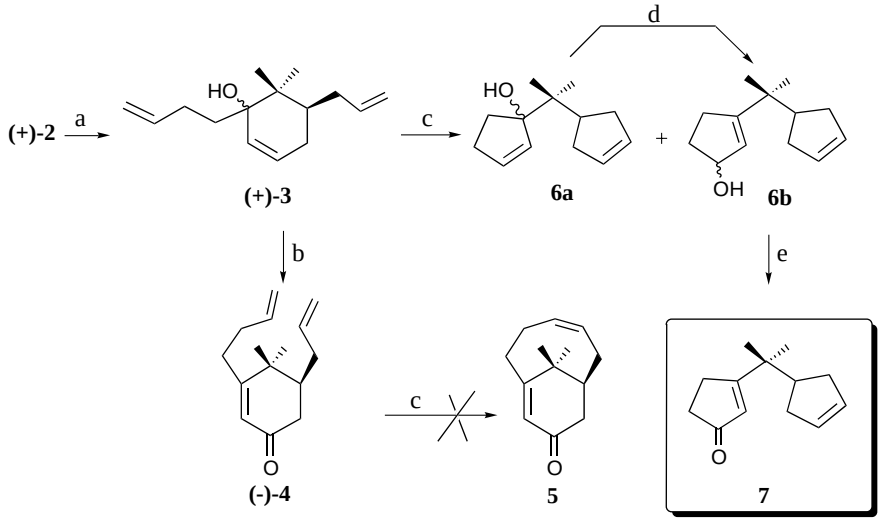
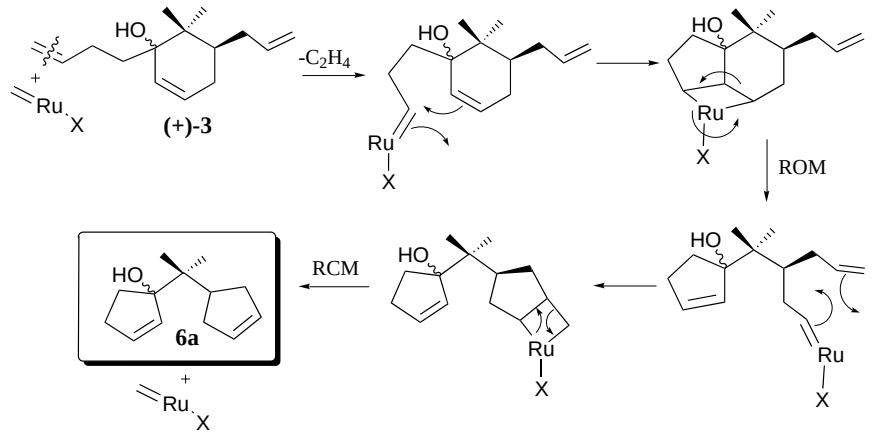


Scheme 2. *Reagents and conditions*: (a) 4-bromo-1-butene, Li, sonication, 75%; (b) PCC, CH_2Cl_2, 93%; (c) Ru[$(PCy_3)_2Cl_2CHPh$] (30 mol%), CH_2Cl_2, 40°C; (d) silica gel, **6a** 6%, **6b** 63%; (e) TPAP, NMMO, CH_2Cl_2, rt, 61%.

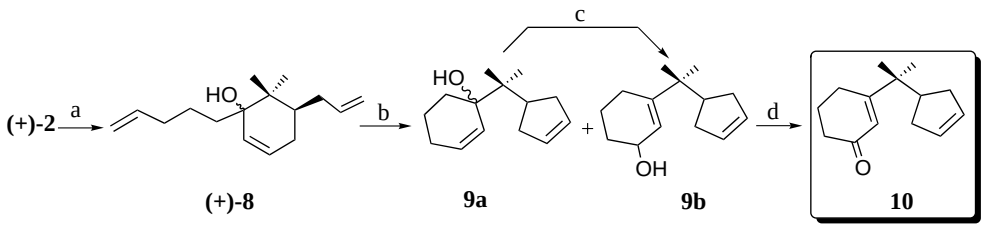


Scheme 3.

the rigidity of the planar cyclohexenone moiety and the unfavorable bridgehead placement of the double bond in the resulting eight-membered ring, we decided to attempt the RCM reaction on the precursor compound (+)-**3**, which was devoid of such difficulties.

Exposure of (+)-**3** to the Grubbs' catalyst Ru[$P(Cy_3)_2$-Cl_2CHPh] produced a very unusual result.[7] On complete consumption of the starting material, the tlc and ^1H NMR screen of the reaction mixture indicated the presence of a major product **6a** along with a small amount of **6b**. When this mixture was passed through a pad of silica gel for purification purposes only **6b** was isolated. Quite clearly, **6a** had converted almost exclusively into **6b** through a facile allylic rearrangement on the silica gel surface. A closer examination of the ^1H and ^{13}C NMR data for the more stable isomer **6b**[8] pointed to the presence of a secondary allylic alcohol unit and a major structural change. To glean further information about the structural reorganization that might have occurred, **6b** was subjected to oxidation with TPAP[9] to yield a single product **7**.[7] The presence of symmetry in **7** as revealed by the ^1H and ^{13}C NMR data (equivalence of the methyls of the *gem*-dimethyl group, two allylic CH_2 groups and two olefinic CH groups) proved to be incisive in arriving at its structure. In addition, the IR value of 1704 cm^{-1} (cyclopentenone carbonyl) and carbon chemical shifts at δ 210 (cyclopentenone carbonyl) and at δ 190 (β-carbon of the cyclopentenone) helped us unambiguously to assign the structure to enone **7**.[8] Thus, based on the structure of **7**, the structures for **6a** and **6b** could be fully secured.

The mechanism of formation of **6a** from (+)-**3** must have involved first the formation of the Ru–carbene intermediate at one of the terminal olefins followed by six-membered ring-opening metathesis (ROM). The newly formed Ru–carbene center now reacts (RCM) with the remaining terminal double bond to afford the di-cyclopentenyl methane derivative **6a**. The most likely sequence operative in the formation of **6a** from **3** is depicted in Scheme 3.



Scheme 4. *Reagents and conditions*: (a) 5-bromo-1-pentene, Li, sonication, 80% (b) $Ru[(PCy_3)_2Cl_2CHPh]$ (30 mol%), CH_2Cl_2, 40°C (c) silica gel, **9a** 8%, **9b** 62% (d) TPAP, NMMO, CH_2Cl_2, rt, 56%.

It was considered appropriate to probe the generality of this novel tandem metathesis reaction. For this purpose, a Barbier reaction was performed on (+)-**2** with 5-bromopentene in the presence of lithium metal to afford the tertiary alcohol (+)-**8** in good yield (Scheme 4). The resulting triene alcohol was exposed to Grubbs' catalyst under conditions identical to those employed for (+)-**3**.[7] In an analogous manner, (+)-**8** also furnished one major product **9a**, which converted to **9b**[8] during purification on a silica gel pad. On oxidation with TPAP,[9] **9a**,**b** afforded the enone **10**[7] whose structure was deduced with the help of ^1H, ^{13}C NMR, IR and MS data[8] which clearly indicated the presence of the cyclohexenone moiety rather than the cyclopentenone moiety (Scheme 4). The symmetry element associated with the formulation **10** was clearly discernible. Structural assignment of **10**, in turn led to the unambiguous formulation of **9a** and **9b**. Mechanistically **9a** can be derived from (+)-**8** in a manner similar to that depicted in Scheme 3.

In summary, we have observed interesting tandem ring-opening/ring-closing metathesis reactions in functionally embellished cyclohexene derivatives in the presence of the Grubbs' catalyst. Such reactions could be employed in a very facile manner, even in a relatively strain-free carbocyclic ring such as the cyclohexenyl ring, to obtain interesting products through deep-seated structural change.

Acknowledgements

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7. Experimental procedure for the tandem ring-closing/ring-opening metathesis reaction of (+)-**3** and (+)-**8**: To a solution of the substrate (+)-**3** (0.045 mmol) in degassed DCM (7 ml) was added dropwise a solution of Grubbs' catalyst (30 mol%) in degassed DCM (3 ml) under an argon atmosphere. The resultant solution was refluxed for 2 h. The solvent was evaporated in vacuo and the residue was loaded on a pad of silica gel. Elution with 1% EtOAc–hexane afforded the less polar product **6a** (6%). Further elution with 5% EtOAc–hexane furnished the more polar product **6b** (63%). Reaction of (+)-**8** with Grubbs' catalyst under identical conditions led to **9a** (8%) and **9b** (62%) after chromatography on silica gel. Procedure for the TPAP/NMMO oxidation of **6b** and **9b**: To a solution of the allylic alcohol **6b** or **9b** (0.007 mmol) in DCM (3 ml) was added NMMO (10 mg, 0.09 mmol) and a pinch of TPAP. The solution was stirred at room temperature for 1 h, diluted with DCM, washed with brine and dried over Na_2SO_4 and concentrated. The crude product was passed through a pad of silica gel and eluted with 5% EtOAc–hexane to afford the enone **7** (61%) or **10** (56%).
8. All new compounds reported here were duly characterized on the basis of spectral [IR, ^1H (2D wherever required) and ^{13}C NMR and MS data] Selected spectral data: **6b**: ^1H NMR (300 MHz, $CDCl_3$): δ 5.62 (2H, s), 5.49 (1H, dd, $J=3.5$, 1.8 Hz), 4.81 (1H, m), 2.54–2.04 (7H, series of m), 1.73–1.64 (2H, m), 1.00 (3H, s), 0.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 129.93, 129.89, 125.5, 77.6, 44.9, 38.2, 34.2, 34.1, 29.8, 28.4, 23.79, 23.77. **7**: IR (neat): 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.97 (1H, t, $J=1.7$ Hz), 5.65 (2H, m), 2.67–2.63 (2H, m), 2.60–2.49 (1H, m), 2.43–2.40 (2H, m), 2.37–2.28 (2H, m), 2.15–2.08 (2H, m), 1.11 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.5, 190.3, 129.8 (2C), 128.8, 45.1, 40.8, 35.3, 34.3 (2C), 28.0, 23.6

(2C); mass (E.I. 70 eV): m/z 191 (M^++1). **9b**: IR (neat): 3368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.62 (2H, s), 5.56 (1H, s), 4.23 (1H, br.), 2.51–2.46 (1H, m), 2.21–1.58 (10H, series of m), 0.95 (3H, s), 0.95 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 129.93, 129.91, 122.5, 66.5, 44.0, 40.4, 34.13, 34.10, 32.1, 24.7, 23.4, 23.1, 19.8. **10**: IR (neat): 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.97 (1H, s), 5.63 (2H, s), 2.59–2.53 (1H, quintet, $J=9$ Hz), 2.40–2.35 (4H, m), 2.30–2.22 (2H, m), 2.12–2.05 (2H, m), 1.98 (2H, quintet, $J=6.3$ Hz), 1.04 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7, 173.1, 129.7 (2C), 124.6, 44.0, 42.1, 37.6, 34.2 (2C), 25.9, 23.4, 22.7 (2C); mass (E.I. 70 eV): m/z 204 (M^+).

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