



Indium mediated γ -pentadienylation of conjugated aldehydes: synthons for hydrindanes by an oxy-Cope–cycloaddition strategy

Alex Melekhov and Alex G. Fallis *

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa ON, K1N 6N5, Canada

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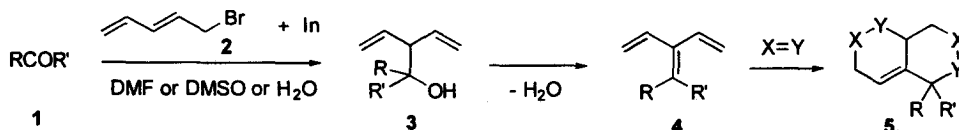
Abstract

The addition of pentadienylindium to unsaturated aldehydes afforded the alcohols **7**, from 1,2-addition, substituted with a 1,4-diene unit. Subsequent anionic oxy-Cope rearrangement provided the Michael 1,4-addition product **8**. Wittig reaction followed by intramolecular [2+4] cycloaddition afforded the hydrindane skeleton in an enantioselective manner (five steps). © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: hydrindanes; indium; intramolecular Diels–Alder reaction.

Allylindium species have received increased study and scrutiny in recent years.¹ These investigations have resulted in a better understanding of the species involved² and led to new synthetic applications. Chemoselectivity and low basicity distinguish these species from their lithium or magnesium counterparts. As is now well established organoindium reagents are stable in aqueous media, and they allow the development of safe and environmentally benign protocols.³

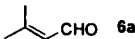
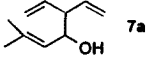

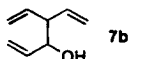
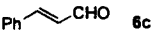
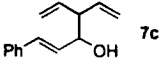
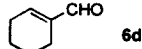
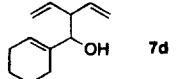
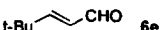
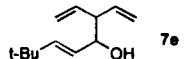
We have established that treatment of 5-bromo-1,3-pentadiene (**2**) with indium metal, in DMF or water, in the presence of carbonyl compounds **1** results in γ -pentadienylation to generate the 1,4-diene-alcohol **3** (Scheme 1).⁴ The exclusive gamma regioselectivity of these condensations is in contrast to many related metallopentadienyl systems such as magnesium in which dimerization products were also present.⁵ Dehydration of the diene-alcohol gave cross-conjugated trienes **4** which reacted rapidly with appropriate dienophiles in a tandem intermolecular Diels–Alder reaction to generate multicyclic systems.⁴



Scheme 1. Pentadienylindium addition–elimination–cycloaddition sequence

* Corresponding author. Tel: (613) 562-5732; fax: (613) 562-5170; e-mail: afallis@science.uottawa.ca

Table 1
Addition of 2,4-pentadienyliindium to unsaturated aldehydes

| Entry | Carbonyl compound | Solvent | Product | Yield ^{a,b} (%) |
|-------|---|------------------|---|--------------------------|
| 1 |  6a | DMF |  7a | 89 |
| 2 | 6a | DMSO | 7a | 91 |
| 3 | 6a | THF | 7a | 40 ^c |
| 4 | 6a | H ₂ O | 7a | 91 |
| 5 | 6a | DMF | 7a | 53 ^d |
| 6 |  6b | DMSO |  7b | 41 |
| 7 |  6c | DMF |  7c | 90 |
| 8 | 6c | DMSO | 7c | 76 |
| 9 |  6d | DMF |  7d | 39 |
| 10 |  6e | DMF |  7e | 67 |

^a isolated yields after workup and silica gel chromatography;

^b products fully characterized by ¹H NMR, ¹³C NMR, IR and HRMS⁹

^c 3 days at rt

^d 1 equivalent of **2** was used

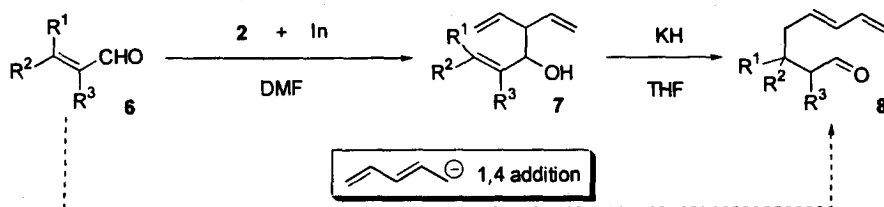
In our study with conjugated aldehydes the indium reagent derived from 5-bromo-1,3-pentadiene reacted exclusively at the carbonyl group in a 1,2 rather than a 1,4 manner to give **7**.

The results from several reactions are summarized in Table 1. The addition of pentadienyliindium was somewhat slower than allyliindium,⁶ requiring normally 12–24 h at 21°C. The preparation of **7** was investigated under various conditions. DMF, DMSO and water were the best solvents although the reaction also proceeded in THF. Generally only 0.5 mL of solvent per 1 mmol of aldehyde was required. The workup procedure was optimized to account for acid sensitivity of products.⁷ The yields are respectable and the material losses are likely due to the susceptibility of the triene unit to polymerization.

Further exploration of the potential of these skipped diene alcohols has established that alcohols of type **7** serve as masked intermediates for the Michael addition of pentadienyl anions to unsaturated aldehydes. This feature has been exploited for the enantioselective construction of a substituted hydrindane skeleton.

The direct 1,4-addition of 2,4-pentadienyl anions to unsaturated aldehydes is usually difficult. These complications arise due to dimerization of halide precursors, and also competitive 1,2 and 1,4 and α - γ additions. A solution to these difficulties could take advantage of the skipped diene alcohols **7** from the initial condensation with unsaturated aldehydes **6**, followed by an oxy-Cope rearrangement of the triene alcohols. This affords a general route to the conjugate addition products, substituted (*E*)-5,7-octadienals of type **8** (Scheme 2). As described below these systems are useful precursors for preparation of substituted bicyclo[4.3.0]nonane skeletons by an intramolecular Diels–Alder reaction⁸ (Scheme 2).

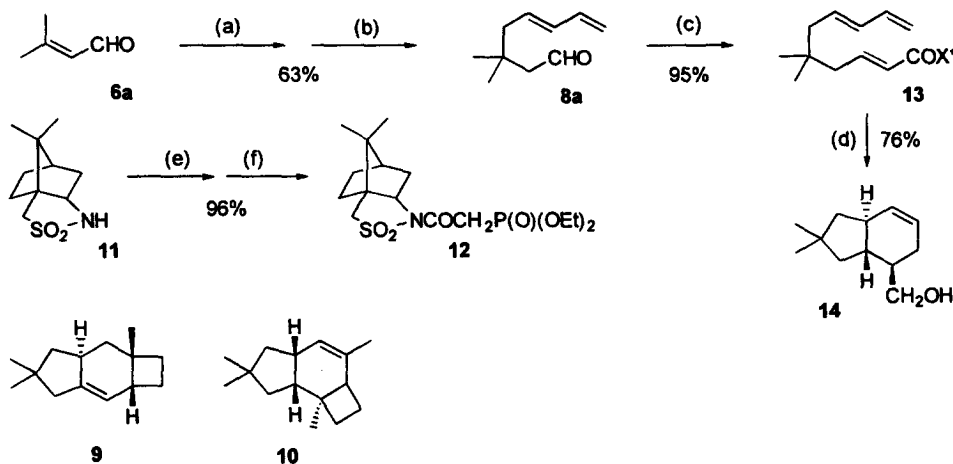
These structural units are important components of many terpenoid natural products. The sesquiterpenes sterpurene^{10a} (**9**) and protoillud-7-ene^{10b} (**10**) both contain a hydrindane core.



Scheme 2. Pentadienylindium addition–[3,3] rearrangement sequence

The anionic oxy-Cope rearrangement of **7a** and **7c** proceeded smoothly in THF at 21°C (KH, 20 min) to provide the β -substituted aldehydes **8a** ($R^1=R^2=Me$, $R^3=H$) and **8c** ($R^1=Ph$, $R^2=R^3=H$) in 67% and 62% yield, respectively ($E:Z>20:1$).

These results have been combined in a convergent enantioselective approach to the hydrindane ring system, based on the following strategy (Scheme 3). Aldehyde **8a** was prepared from 3-methyl-2-butenal (**6a**) in 63% yield (2 steps, 10 mmol scale). The Oppolzer chiral auxiliary was employed to render the intramolecular Diels–Alder reaction enantioselective.¹¹ (1*S*)-(–)-2,10-Camphorsultam (X^*H) (**11**) was acylated with bromoacetyl bromide and the resulting bromo-amide reacted with triethylphosphite at 120°C to form phosphonate **12** in 96% yield. Treatment of **12** with DBU and LiCl in the presence of the aldehyde **8a** afforded the enamide **13** in 95% yield ($E:Z=20:1$).¹² The cycloaddition was effected by treatment of **13** with methylaluminum dichloride in methylene chloride at –20°C followed by cleavage of the camphorsultam upon reduction with LiAlH₄. Workup provided the enantiomerically pure adduct **14** in 76% yield.



Scheme 3. Enantioselective construction of the hydrindane skeleton. Reagents and conditions: (a) **2**, In, DMF, 21°C, 12 h; (b) KH, THF, 0–5°C; (c) **12**, DBU, LiCl, CH₃CN, 21°C, 4 h; (d) 1) MeAlCl₂, CH₂Cl₂, –20°C, 5 h, 2) LAH, Et₂O, 21°C; (e) NaH, BrCH₂COBr, PhMe, 0–5°C; (f) (EtO)₃P, 120°C, 1 h

In summary, the 1,2-carbonyl addition of the 2,4-pentadienylindium reagent to unsaturated aldehydes affords the conjugate addition product after [3,3]-sigmatropic rearrangement. This sequence constitutes an alternative method for the synthesis of the 1,4 addends. Subsequent addition of a chiral dienophile followed by intramolecular [2+4] cycloaddition provides a direct entry to the hydrindane skeleton. The extension of these protocols is under further investigation.

Acknowledgements

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- Representative experimental procedure: Indium (1.3 mmol) was added to a stirred solution of aldehyde (2 mmol) and 5-bromo-1,3-pentadiene (4 mmol) in DMF (1 mL) under nitrogen atmosphere at 0–5°C and the resulting mixture was stirred for 16–20 h. Then it was diluted with wet ether (20 mL) stirred for an additional 5 min and dried with MgSO₄. Concentration followed by flash silica gel chromatography furnished skipped diene alcohol.
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- Selected spectroscopic data: **7a**: ¹H NMR (CDCl₃) δ 1.66 (s, 3H), 1.71 (s, 3H), 2.80–2.85 (m, 1H), 4.24 (dd, *J*=9.0, 6.9 Hz, 1H), 5.06–5.19 (m, 5H), 5.74–5.82 (m, 2H); ¹³C NMR (CDCl₃) δ 18.5, 25.8, 55.0, 70.1, 116.7, 117.7, 125.1, 136.6, 137.0, 137.1; IR (neat) cm⁻¹ 3380, 3080, 1635; HRMS *m/z* (M–H₂O)⁺: 134.1083; calcd for C₁₀H₁₄: 134.1096; **8a**: ¹H NMR (CDCl₃) δ 1.03 (s, 6H), 2.08 (d, *J*=7.7 Hz, 2H), 2.23 (d, *J*=3.0 Hz, 2H), 4.97 (d, *J*=10.2 Hz, 1H), 5.09 (d, *J*=17.0 Hz, 1H), 5.66 (dt, *J*=15.0, 7.7 Hz, 1H), 6.02 (dd, *J*=15.0, 10.4 Hz, 1H), 6.28 (ddd, *J*=17.0, 10.4, 10.2 Hz, 1H), 9.80 (t, *J*=3.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 27.3, 34.2, 45.6, 54.4, 115.7, 130.2, 134.3, 136.8, 203.1; IR (neat) cm⁻¹ 3085, 2960, 1720; HRMS *m/z* (M⁺): 152.1220; calcd for C₁₀H₁₆O: 152.1202; **14**: ¹H NMR (CDCl₃) δ 1.02 (s, 3H), 1.03 (s, 3H), 1.08–1.13 (m, 1H), 1.21 (br s, 1H), 1.30–1.39 (m, 1H), 1.59–1.63 (m, 1H), 1.68–1.77 (m, 1H), 1.81–1.88 (m, 1H), 2.04–2.13 (m, 1H), 2.22–2.28 (m, 1H), 3.47 (dd, *J*=10.6, 6.6 Hz, 1H), 3.62 (dd, *J*=10.6, 4.8 Hz, 1H), 5.56–5.60 (m, 1H), 5.72 (dd, *J*=9.9, 1.4 Hz, 1H); HRMS *m/z* (M⁺): 180.1527; calcd for C₁₂H₂₀O: 180.1515.
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