Total Synthesis of (+)-Taylorione utilising Modified Pauson–Khand Reaction Methodology

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A total synthesis of the sesquiterpene, (+)-taylorione **1** starting from (+)-2-carene is described; the key synthetic transformation is achieved in high yield by application of developed Pauson–Khand reaction techniques for gaseous olefins.

(+)-Taylorione **1** is the enantiomer of the principal sesquiterpene isolable from the liverwort *Mylia taylorii*.[1] The connectivity and absolute configuration were determined by spectroscopic and degradative techniques,[2] and have been confirmed by an unfortunately inefficient and laborious synthesis.[3] In this communication, we report the concise enantiospecific total synthesis of (+)-taylorione from readily available starting materials. The synthetic strategy towards this target incorporates a novel and useful extension of Pauson–Khand reaction protocol,[4] which affords cyclopentenones from the reaction of alkenes with alkynehexacarbonyldicobalt complexes.

Until now, when gaseous olefins or volatile alkenes were employed in the Pauson–Khand reaction, conditions of elevated temperature and pressure have been required to obtain only moderate yields of cyclopentenones.[5] Our findings, which will be published in full elsewhere, show that the application of trimethylamine *N*-oxide dihydrate[6] to alkynehexacarbonyldicobalt complexes in the presence of ethylene even at atmospheric pressure gives rise to similar yields of cyclopentenone products within 24 h. Moreover, an approximately twofold increase in yield can generally be realised in the annulation reactions by the application of the systematically optimised conditions of: 25–30 atm of ethylene, 9 equiv. of $Me_3N^+O^-\cdot 2H_2O$ at 40 °C in MeOH–toluene (1 : 1). This novel extension of Pauson–Khand methodology has been successfully incorporated into the enantiospecific synthesis of (+)-taylorione in the manner laid out in Scheme 1.‡

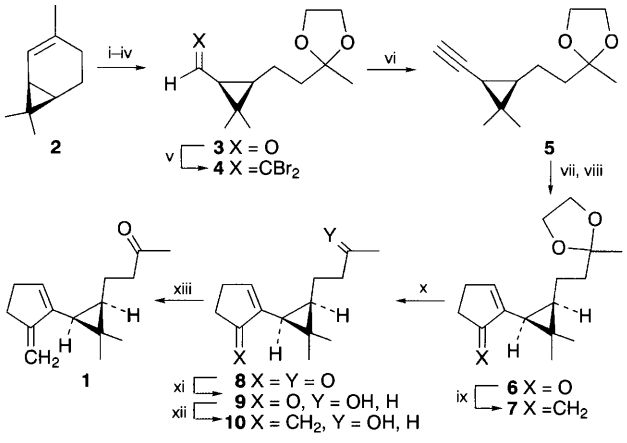
Aldehyde **3** was obtained from commercially available (+)-2-carene **2** using an amended procedure.[7] The dibromoolefin **4** resulting from a Wittig-type process was converted to the terminal alkyne **5** without complication.[8] The requisite hexacarbonyldicobalt complex was readily prepared in quantitative yield at room temp. as the desired precursor for the pivotal Pauson–Khand annulation reaction. Subjecting this complex to the conditions described above furnished cyclopentenone **6** in an excellent yield (81%), while simply bubbling ethylene through a mixture of the cobalt complex and $Me_3N^+O^-\cdot 2H_2O$ in MeOH–toluene afforded the same product in a more modest yet acceptable yield.§

A series of carbonyl methylenation studies found that Peterson olefination in the presence of $CeCl_3$[9] was the most successful method of obtaining the desired diene **7**. Unfortunately, extensive synthetic effort failed to identify conditions which would convert **7** into (+)-taylorione **1**. General decomposition of **7** and alkene isomerisation thwarted clean ketal hydrolysis even under the most mild conditions. To circumvent this problem, whilst retaining the largely successful strategy used up to this point, the ketal present in **6** was deprotected[10] and the resulting carbonyl **8** was selectively reduced[11] to afford the hydroxy enone **9**. Methylenation, using the same technique as previously, was followed by application of the mild Griffith–Ley reagent, tetrapropylammonium perruthenate (TPAP),[12] as oxidising agent to give (+)-taylorione **1**, identical in spectroscopic data with the natural material, in high optical purity.¶

This enantiospecific synthesis of (+)-taylorione **1** from a readily available chiral pool reagent is achieved in an excellent overall yield of 9% over 12 synthetic transformations and forms part of an ongoing effort to efficiently apply transition metals in organic synthesis.

The SERC is gratefully acknowledged for a studentship (C. J.) and we thank the EC (U. L.) for support.

Received, 6th December 1994; Com. 4/07465C



Scheme 1 *Reagents and conditions*: i, O_3, MeOH, −78 °C → room temp. then H_2O_2, NaOH, reflux (60%); ii, ethylene glycol, benzene, *p*-TSA, reflux (100%); iii, LAH, ether, room temp. (90%); iv, PDC, CH_2Cl_2, room temp. (73%); v, PPh_3 (4 equiv.), CBr_4 (1 equiv.), CH_2Cl_2, 0 °C (84%); vi, BuLi (2 equiv.), THF, −78 °C → room temp., H_2O (100%); vii, $Co_2(CO)_8$, light petroleum, room temp. (100%); viii, C_2H_4 (25 atm.) $Me_3N^+O^-\cdot 2H_2O$ (9 equiv.), MeOH–toluene (1 : 1), 40 °C (81%) or C_2H_4 (bubbling, 1 atm, $Me_3N^+O^-\cdot 2H_2O$ (9 equiv.), MeOH–toluene (1 : 1), room temp. (41%); ix, Me_3SiCH_2Li, $CeCl_3$, THF, −78 °C → room temp. then aqueous HF (70%) or SiO_2 (58%); x, $TiCl_4$, diethyl ether, 0 °C (79%); xi, $NaBH_4$, CH_2Cl_2 and 5% MeOH, AcOH (89%); xii, Me_3SiCH_2Li, $CeCl_3$, THF, −78 °C → room temp. then SiO_2 (47%); xiii, TPAP, *N*-methylmorpholine *N*-oxide, crushed molecular sieves, CH_2Cl_2 (91%)

Footnotes

† Participating in the ECTS-Pilot Scheme of the EC Erasmus Programme. Resident University: Institut für Organische Chemie der Technischen Universität Berlin, Strasse des 17. Juni 135, 10623 Berlin, Germany.

‡ All compounds exhibited satisfactory analytical and spectral data.

§ More classical Pauson–Khand cyclisation techniques of higher temperature and pressure [C_2H_4 (50 atm) at 80 °C in benzene] gave a modest yield of 38%.

¶ $[\alpha]^{20}_D$ + 27.4 (*c* 0.84, $CHCl_3$) for **1**. Lit.[2] $[\alpha]^{20}_D$ −28.1 (*c* 1.52, $CHCl_3$) for (−)-taylorione.

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