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Stereocontrolled total syntheses of (±)-clovan-3-one and (±)-*epi*-clovan-3-one and a facile total synthesis of (±)-pseudoclovene-A

Tapas Paul and Debabrata Mukherjee*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Calcutta-700 032, India

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Abstract—Stereocontrolled total syntheses of the bridged tricyclic ketones (±)-clovan-3-one (**5**) and (±)-*epi*-clovan-3-one (**6**) and a facile total synthesis of the tricyclic sesquiterpene (±)-pseudoclovene-A (**3**) have been successfully accomplished involving participation of an aryl intramolecular cyclisation of the bromophenol **11** as a key step.

Tricyclic sesquiterpenes derived from acid treatment of caryophyllene and caryolan-1-ol possess novel skeletal features and have attracted considerable attention as challenging synthetic targets. Clovene (**1**)[1] and *epi*-clovene (**2**)[2] are acid-catalysed rearrangement products of caryophyllene and caryolan-1-ol, respectively. The sesquiterpenes **1** and **2** incorporate a tricyclo[6.3.1.0^{1,5}]-dodecane ring system as the basic carbocyclic framework but differ in the stereochemistry of the A/B ring junction which is *cis* in **1** and *trans* in **2** (Fig. 1). Pseudoclovene-A (**3**), another sesquiterpene hydrocarbon possessing a similar tricyclo[6.3.1.0^{1,5}]dodecane skeleton was isolated[3] along with several other sesquiterpenes when caryolan-1-ol was treated with polyphosphoric acid. On the basis of chemical and spectroscopic studies, the structure **3** was proposed for pseudoclovene-A and this structure was conclusively established by synthesis[3] as well as through X-ray crystallographic analysis[3] of the *p*-bromobenzenesulfonate ester **4** (Fig. 1) which was prepared from **3**. The possible mode of formation of **2** and **3** from caryolan-1-ol was investigated by Parker and co-workers and a plausible mechanistic scheme was proposed.[2] The total synthesis of the sesquiterpenes **1** and **2** must address the following problems: (i) construction of the tricyclo[6.3.1.0^{1,5}]dodecane framework with appropriate substituents at C-4 and C-8, (ii) control of the stereochemistry of the A/B ring junction, and (iii) introduction of an isolated double bond in ring A. Although clovene (**1**) has been synthesised[4] a number of times, the synthesis of *epi*-clovene (**2**) has not been reported yet in the literature. Starting from 2,5-dimethyl-6-methoxy-1-tetralone (**7**),[5] we report here an aryl cyclisation strategy to accomplish a stereocontrolled total synthesis of the bridged tricyclic ketones (±)-clovan-3-one (**5**) and (±)-*epi*-clovan-3-one (**6**). During the present studies, we have also accomplished a facile total synthesis of (±)-pseudoclovene-A (**3**) as shown in Scheme 1. The salient

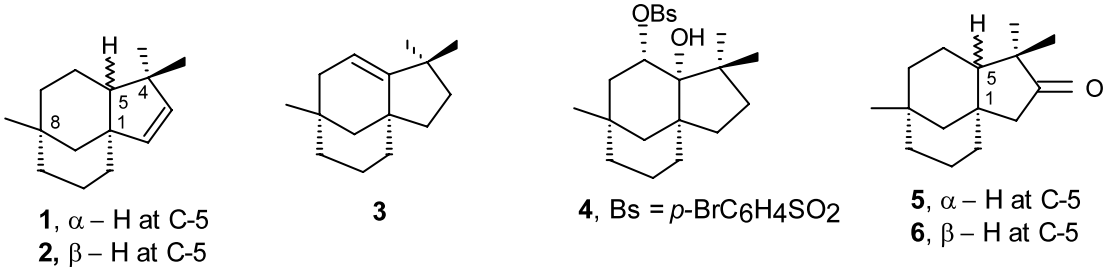

Figure 1.

Keywords: terpenes; ketones; cyclisation; hydrogenation; alkylation.

* Corresponding author. Fax (91)-33-2473-2805; e-mail: ocdm@mahendra.iacs.res.in

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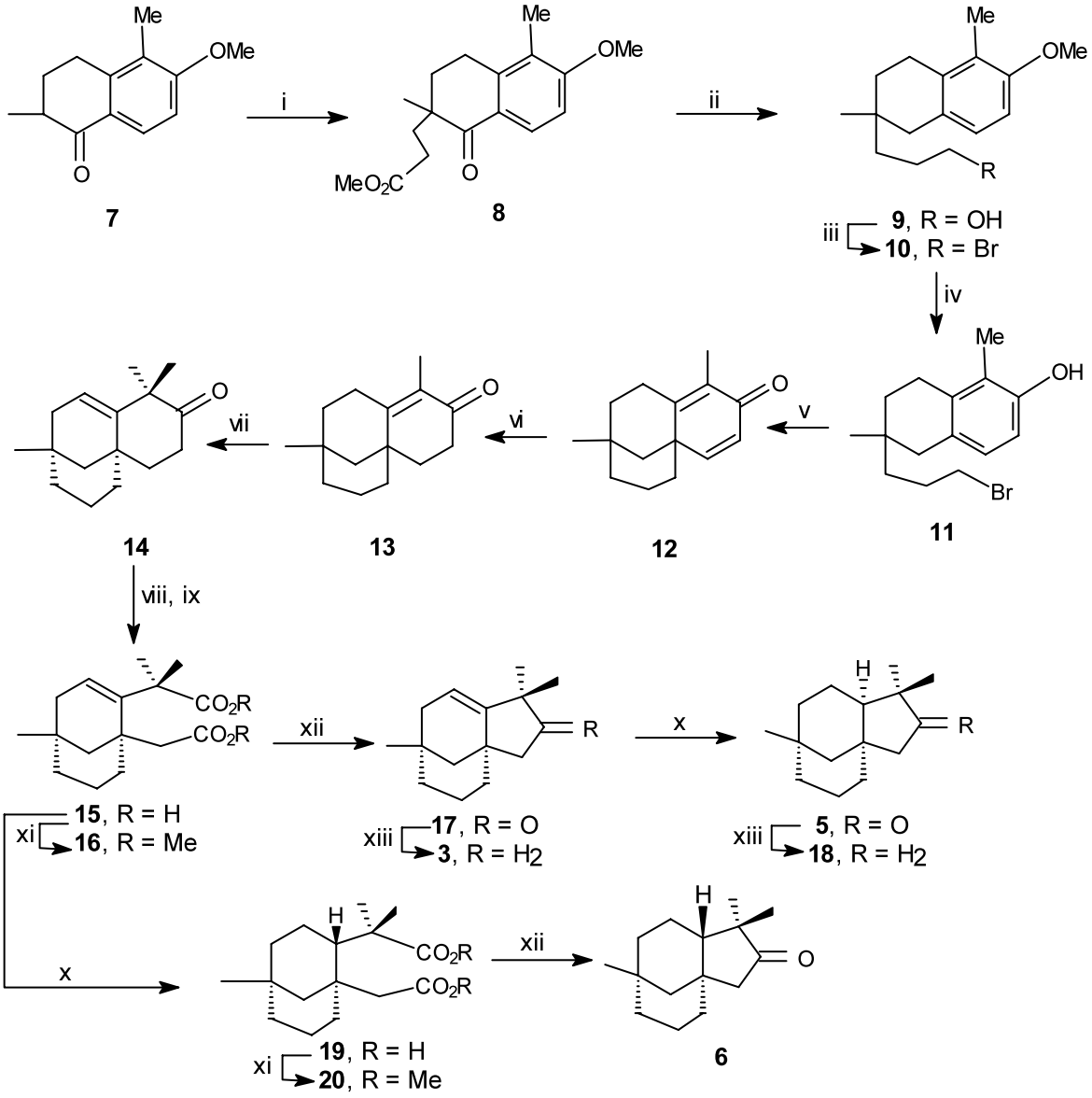

Scheme 1. *Reagents and conditions*: (i) CH_2=$CHCO_2Me$, *t*-BuOK, *t*-BuOH, reflux, 78%; (ii) $LiAlH_4$, Et_2O, reflux then Li, liq. NH_3, EtOH, 75%; (iii) PBr_3, C_6H_6, 0–70°C, 75%; (iv) BBr_3, CH_2Cl_2, 0°C to rt, 90%; (v) *t*-BuOK, *t*-BuOH, reflux, 62%; (vi) H_2, $[(C_6H_5)_3P]_3Rh(I)Cl$, EtOH, C_6H_6, rt, 91%; (vii) Me_2EtCOK, C_6H_6, 70°C; MeI, 0°C to reflux, 86%; (viii) NaH, HCO_2Et, C_6H_6, 5°C to rt, 88%; (ix) aq. NaOH, H_2O_2, 0°C to rt, H_3O^+, 81%; (x) H_2, 10% Pd–C, AcOH, rt, 94% (**15**→**19**) and 90% (**17**→**5**); (xi) CH_2N_2, Et_2O, 0°C, 95%; (xii) *t*-BuOK, C_6H_6, reflux, H_3O^+; DMSO, NaCl, H_2O, 155°C, 70% (**16**→**17**) and 65% (**20**→**6**); (xiii) N_2H_4, $N_2H_4{\cdot}2HCl$, $(HOCH_2CH_2)_2O$, 125°C; KOH, 220°C, 75% (**17**→**3**) and 73% (**5**→**18**).

features of our synthesis are (i) efficient conversion of the tetralone **7** into the bromophenol **11**, (ii) an aryl based intramolecular cyclisation of **11** in the presence of base to provide the tricyclic dienone **12** in good yield, (iii) facile conversion of **12** into the diesters **16** and **20** via the enone **14**, and (iv) stereocontrolled transformation of **16** into clovanone (**5**) via the enone **17** and transformations of **20** and **17** into *epi*-clovanone (**6**) and pseudoclovene-A (**3**), respectively. Funk and co-workers converted[4] (±)-clovanone (**5**) into (±)-clovene (**1**) via the Shapiro reaction.

Our synthesis of **3**, **5** and **6** from **7** is outlined in Scheme 1. Michael reaction of the tetralone **7** with methyl acrylate in the presence of *t*-BuOK in *t*-BuOH afforded the ketoester **8**[6] in 78% yield. Reduction of **8** with $LiAlH_4$ followed by hydrogenolysis of the benzylic hydroxyl group of the resulting diol with lithium in liquid ammonia furnished the primary alcohol **9** in 75% overall yield. Treatment of **9** with PBr_3 provided the bromoether **10** (75%) which was demethylated with BBr_3 to afford the bromophenol **11** (90%). An aryl based intramolecular cyclisation[7] of **11** was effected by refluxing with *t*-BuOK (1 equiv.) in *t*-BuOH to furnish the tricyclic dienone **12**[8] in 62% yield. Selective catalytic hydrogenation of the disubstituted double bond of the dienone **12** in the presence of $[(C_6H_5)_3P]_3RhCl$ provided the enone **13** (91%). Methylation of **13** employing

potassium *t*-amylate as the base furnished the β,γ-unsaturated ketone **14** in 86% yield. The ketone **14** was condensed with ethyl formate in the presence of NaH and the resulting hydroxymethylene derivative was treated[9] with alkaline H_2O_2 to give the unsaturated diacid **15** as a crystalline compound in 81% yield. Catalytic hydrogenation of **15** in AcOH yielded the diacid **19** as the only product (94%). The structures of the diacids **15** and **19** and the relative stereochemistries at C-1, C-2 and C-5 of **19** were conclusively established by single crystal X-ray crystallography.[10] Treatment of the diacids **15** and **19** with ethereal CH_2N_2 afforded the diesters **16** and **20** in near quantitative yields.

Dieckmann cyclisation of the diester **16** followed by decarbomethoxylation of the resulting β-ketoester provided the enone **17** (70%). Huang-Minlon reduction of **17** furnished (±)-pseudoclovene-A (**3**) (75%). The spectral data of **3** agreed very well with those reported in the literature.[3] Catalytic hydrogenation of the enone **17** in AcOH under appropriate experimental conditions[11] furnished the *cis*-fused ketone (±)-clovan-3-one (**5**) as the sole product in 90% yield. The *cis*-stereochemistry of the A/B ring junction of the present compound was confirmed through conversion of **5** into (±)-clovane (**18**) (73%) by Huang-Minlon reduction. The ^{1}H NMR data of **18** were in excellent agreement with those reported[12] for clovane. It may be mentioned in this connection that catalytic hydrogenation of closely related systems had generated[13–16] exclusively *cis*-stereochemistry at 6/5 ring junctures. Also, Parker and co-workers observed[2] that catalytic hydrogenation of pseudoclovene-A (**3**) furnished the *cis*-fused hydrocarbon clovane (**18**) as the only product. As mentioned before, clovanone (**5**) was converted[4] into clovene (**1**) via the Shapiro reaction.

Dieckmann cyclisation[17] of the diester **20** and subsequent decarbomethoxylation of the resulting β-ketoester afforded the bridged tricyclic ketone (±)-*epi*-clovan-3-one (**6**) in 65% yield. The transformation of **6** into (±)-*epi*-clovene (**2**) is under active pursuit.

In conclusion, stereocontrolled total syntheses of the bridged tricyclic ketones (±)-clovan-3-one and (±)-*epi*-clovan-3-one and a facile total synthesis of the tricyclic sesquiterpene (±)-pseudoclovene-A have been successfully accomplished involving aryl based intramolecular cyclisation of an appropriately substituted bromophenol, a tetrahydronaphthalene derivative, as a key reaction. The present synthesis of clovan-3-one constitutes a formal total synthesis of (±)-clovene.

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