Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6159-6162, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01424-X

Polyene Cyclization Promoted by the Cross Conjugated α-Carbalkoxy Enone System. Application to the Total Synthesis of (±)-Dehydrochamaecynenol

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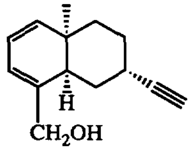
Abstract: The title cyclization process has been effectively applied to the first total synthesis of dehydrochamaecynenol in racemic form. © 1997 Elsevier Science Ltd.

During the course of our synthetic studies on clerodanes,[1,2] it was serendipitously discovered that the cross conjugated α-carbalkoxy enone system could serve as a highly effective promoter for cationic cyclization, which occurred readily with high regio- and stereoselectivity, and also with an unusual termination process involving chlorine incorporation when a metal chloride was used as the reagent.[3] In essence, this cyclization process allows for expeditious construction of polycyclic compounds with a high level of functionalization, and thus is expected to have broad utility in the synthesis of polycyclic natural products, especially those of the isoprene origin. In this communication, we wish to report the successful application of this newly developed polyene cyclization process to facilitate the total synthesis, in racemic form, of dehydrochamaecynenol (**1**),[4] a natural alcohol isolated from *Chamaecyparis formosensis* Matsum. Cupressaceae about thirty years ago. The structure of this norsesquiterpenoid, which has not been synthesized previously, was deduced mainly based on spectroscopic methods. The unambiguous total synthesis described herein serves also to confirm the structural assignment.

Scheme 1



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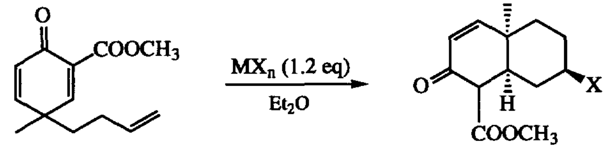

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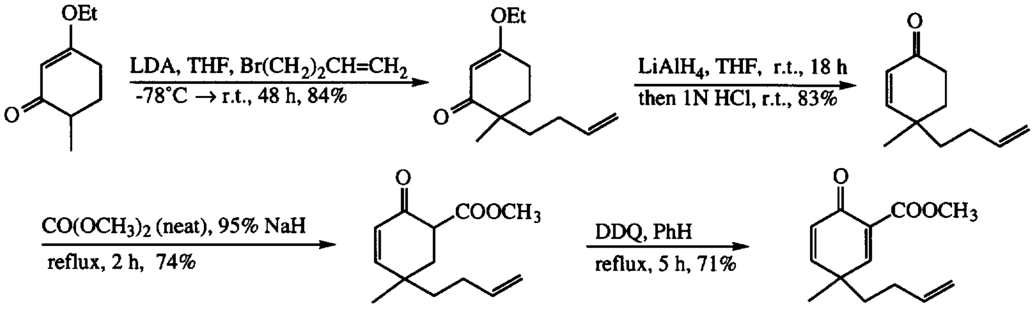
AlCl$_3$, -78°C, 15 min, 75% **3** X=Cl
ZnI$_2$, r.t., 72 h, 85% **4** X=I



2

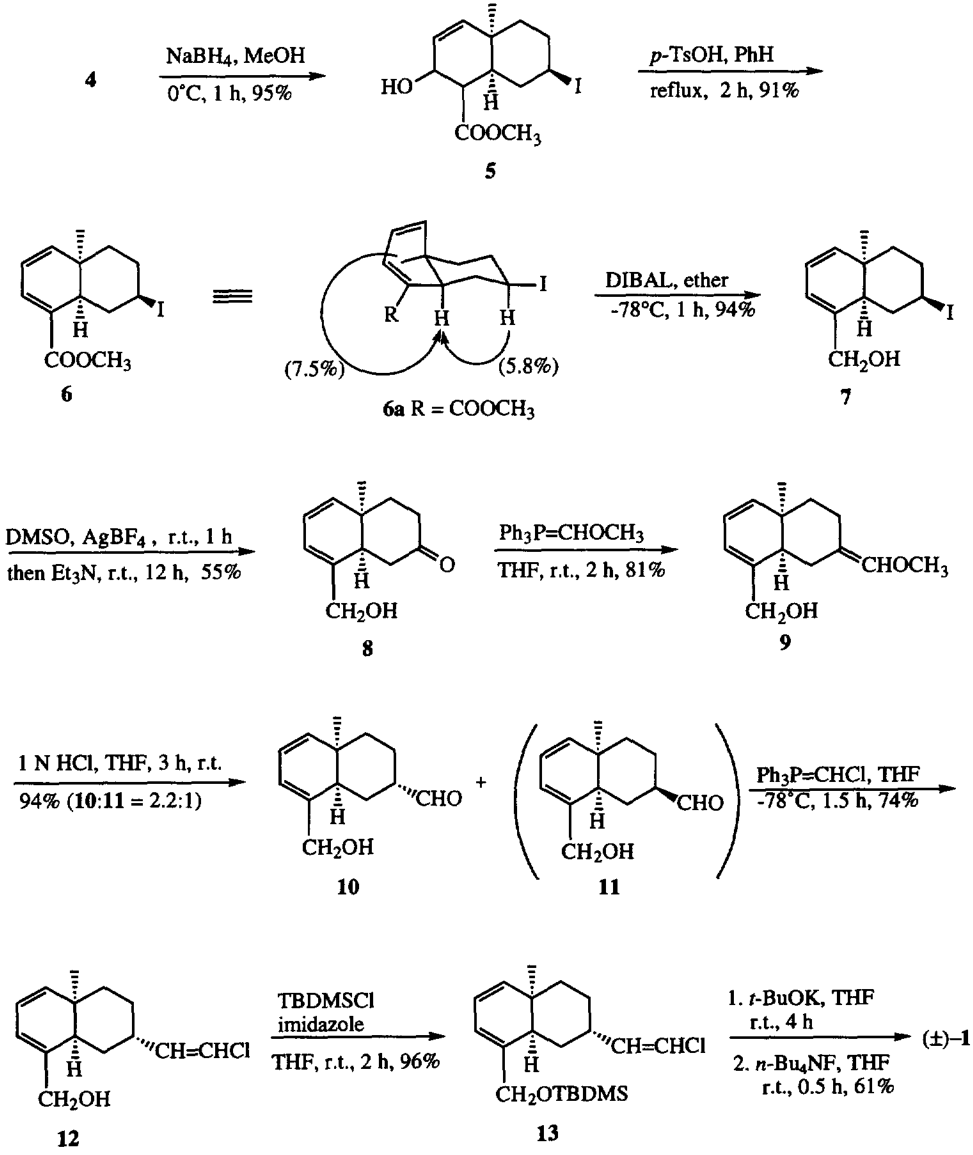
Scheme 2

The synthesis began with enone ester **2** which was shown previously to undergo facile cyclization on exposure to aluminum chloride, giving rise to the bicyclic chloride **3** in good yield[3] (Scheme 1). The preparation of enone ester **2** from 3-ethoxy-6-methyl-2-cyclohexenone[5] has since been improved via a sequence involving four synthetic operations (Scheme 2): alkylation with 4-bromo-1-butene, lithium aluminum hydride reduction followed by acidic work-up, carbomethoxylation, and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[6] As well, the cyclization has been made more effective. When enone ester **2** was treated with zinc iodide in ether at room temperature for three days, iodide **4**, which contains suitable functional groups at strategic positions for rapid construction of the target compound **1**, was formed in 85% yield.

Iodide **4** proved to be a highly effective synthetic intermediate (Scheme 3). Reduction of **4** with sodium borohydride in methanol at 0°C gave a diastereomeric mixture of two hydroxy esters **5**. Treatment of this mixture with *p*-toluenesulfonic acid in refluxing benzene furnished diene ester **6**, the stereochemistry of which was confirmed by nOe experiments (see **6a**). Diene ester **6** was subsequently reduced with diisobutylaluminum hydride in ether at -78°C to give iodo alcohol **7** in 81% yield over three steps. Iodo alcohol **7** was directly oxidized to the corresponding hydroxy ketone **8** (55% yield) using a combination of dimethyl sulfoxide, silver tetrafluoroborate and triethylamine.[7]

To install the acetylene unit,[8] ketone **8** was subjected to a Wittig reaction with methoxymethylenetriphenylphosphorane.[9] The isomeric enol ethers **9** (3:2) thus obtained in 81% yield were subsequently hydrolyzed with 1N hydrochloric acid under kinetic conditions (room temperature, 3 h) to give predominantly aldehyde **10** (65% yield) along with the thermodynamically more stable aldehyde **11** (29% yield). The latter aldehyde was formed in increasing amount at the expense of the former when the hydrolysis reaction was prolonged. As well, treatment of aldehyde **10** with sodium hydroxide in methanol resulted in the exclusive formation of its epimer **11**.

The conversion of aldehyde **10** to the target molecule **1** was carried as follows. Treatment of **10** with chloromethylenetriphenylphosphorane[10] in tetrahydrofuran at -78°C for 1.5 h resulted in the formation of two isomeric vinyl chlorides in 74% yield. Direct transformation of **12** into compound **1** was attempted using potassium *tert*-butoxide[10] and *n*-butyllithium.[11] However, in each case, a complex mixture was produced, apparently due to complications caused by the presence of the hydroxy group. Consequently, the hydroxy group was protected by treatment of **12** with *tert*-butyldimethylsilyl chloride and imidazole. Silyl ethers **13** thus obtained in virtually quantitative yield were subjected to dehydrochlorination with potassium *tert*-butoxide in tetrahydrofuran at room temperature, and the racemic dehydrochamaecynenol (**1**) was isolated in 61% yield[12] following the removal of the silyl protecting group using tetra-*n*-butylammonium fluoride. The spectral data (IR, ^{1}H NMR and mass spectra) of the synthetic material[15] were found to be in good agreement with those reported for the naturally occurring compound (-)-**1**.[4]



Scheme 3

Acknowledgment: We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support.

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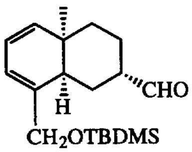
12. In another approach to **1**, compound **10** was first converted (TBDMSCl, imidazole, THF, r.t., 4 h) to the corresponding *tert*-butyldimethylsilyl ether **i**. This was followed by a Wittig reaction[13,14] (triphenylphosphine, carbon tetrabromide, CH_2Cl_2, 0°C, 0.5 h) to give dibromide **ii**, which was transformed into (±)-dehydrochamaecynenol by sequential treatment with *n*-butyllithium[13,14] (THF, -78°C, 1 h) and tetra-*n*-butylammonium fluoride (THF, r.t., 1 h). This approach was inferior in terms of overall yield (5% from **10**).



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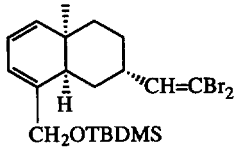

ii

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15. IR (CH_2Cl_2): 3390, 3308, 3030, 2120, 1650, 1050, 726 cm^{-1}; ^1H NMR (400Hz, $CDCl_3$): δ 5.92 (dd, J = 9, 5 Hz, 1H), 5.85 (d, J = 5 Hz, 1H), 5.45 (d, J = 9 Hz, 1H), 4.15 (s, 2H), 2.78 (m, 1H), 2.19 (ddd, J = 11, 4.5, 1.5 Hz, 1H), 2.07 (d, J = 2.5, 1H), 1.95-1.00 (complex, 6H), 0.95 (s, 3H); HRMS: calcd. for $C_{14}H_{18}O$: 202.1358; found: 202.1361.

(*Received in USA* 12 *June* 1997; *revised* 7 *July* 1997; *accepted* 10 *July* 1997)