Tetrahedron Letters, Vol. 34, No. 37, pp. 5947-5950, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Pd^{2+}-Promoted Cyclization in Tetracyclic Diterpene Synthesis Highly Diastereoselective Formal Total Synthesis of (±)-Stemodin

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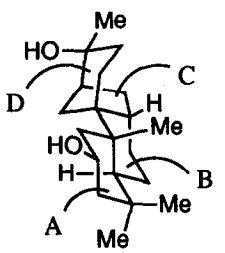
Abstract: Intramolecular Diels-Alder reaction of the triene **5** and Pd^{2+}-promoted cyclization reaction of the olefinic silyl enol ether of **10** have been utilized as the key steps for a conceptually new, highly diastereocontrolled formal total synthesis of (±)-stemodin (**1**).

The tetracyclic diterpenes stemodin (**1**)[1] and aphidicolin (**2**)[2] have attracted attention owing to their interesting biological properties[3] and to their challenging CD ring system, constituted by a bicyclo[3.2.1]-octane moiety.



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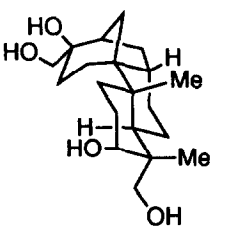

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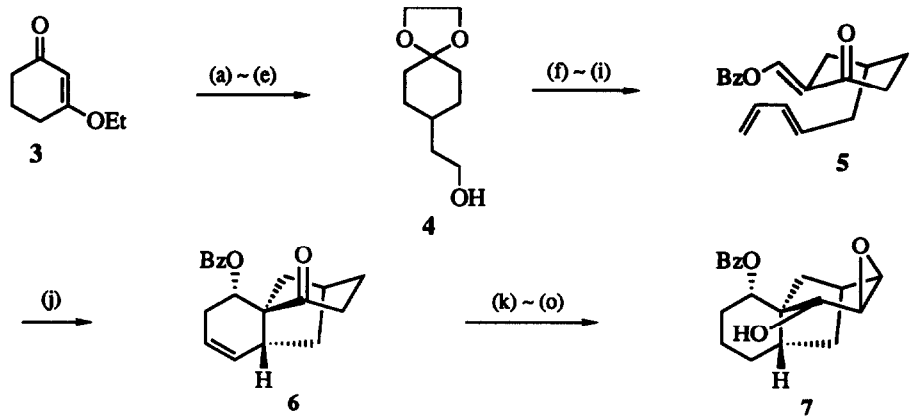
We outline herein a synthesis of the racemate of **1** by an approach which includes several unique steps: (i) intramolecular Diels-Alder reaction[4] of the triene **5** for the construction of the BCD ring system, (ii) 1, 3-carbonyl transposition reaction *via* a radical-mediated epoxide fragmentation (**7**→**8**),[5] and (iii) Pd^{2+}-promoted highly diastereoselective cyclization reaction (**10**→**12**).[6] The presently described route is based on a line of analysis which is conceptually different from that for the reported syntheses[7] of (±)-**1**. The central feature of our strategy is a construction of the spiro fused bicyclo[3.2.1]octane ring system *via* intramolecular Diels-Alder reaction of **5** as described in our prior model studies.[4] The choice of this strategy was dictated by the need to control the diastereoselective construction of the AB *trans* ring juncture of **1** using a Pd^{2+}-promoted cyclization reaction. We felt that establishment of the required relative stereochemistry about the AB ring system could be conveniently achieved utilizing the rigid template. The execution of this synthesis

proceeded as summarized in Schemes I and II.

Scheme I



(a) LDA, THF, -78 °C; $BrCH_2CO_2Et$, -45 °C, (b) LAH, THF, (c) 1N HCl, THF, (d) H_2, 10% Pd-C, EtOAc, (e) $HOCH_2CH_2OH$, TsOH, C_6H_6, ref, (f) SO_3·Py, DMSO, Et_3N, (g) $Ph_2P(O)CH_2CH{=}CH_2$, ^nBuLi, HMPA,THF, (h) 10% $HClO_4$, THF, (i) NaH, C_6H_6; HCO_2Et; Bz_2O, Py, (j) 280 °C, *o*-dichlorobenzene, (k) H_2, 10% Pd-C, EtOAc, (l) $C_5H_5N^+HBr_3^-$, AcOH, (m) DBU, C_6H_6, (n) 30% H_2O_2, NaOH, (o) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH.

3-Ethoxy-2-cyclohexen-1-one (**3**) was converted to the alcohol **4** in the usual manner[8] (59 % overall yield), which upon Parikh modified Moffatt oxidation,[9] Yamamoto's olefination,[10] deprotection (66 % from **4**), and methylenation (89 %) afforded **5**.

In order to construct the spiro fused bicyclo[3.2.1]octane derivative **6**, the Lewis acid catalyzed intramolecular Diels-Alder reaction of **5** was first attempted under the various conditions, giving the unsatisfactory result even by the use of Me_2AlCl as a catalyst.[11] However, the thermal reaction in *o*-dichlorobenzene at 280 °C (3 h) proceeded quite nicely to provide **6** (62%), together with its stereoisomer in a ratio of 16 : 1,[12] whose structure was determined by X-ray analysis.[4] Our synthetic efforts were next focused on the 1, 3-transposition reaction of carbonyl group in **6**. After numerous attempts,[13] an approach by radical-mediated epoxide fragmentation[5] of the thionoimidazolide of **7**, prepared from **6** in 6 steps {(i) hydrogenation (86 %), (ii) bromination (88 %), (iii) elimination (85 %), (iv) epoxidation (88 %), reduction (94 %), and thioesterifi-cation (88 %)}, was found to give rise to the desired product in good yield (79 %). Protection (96 %) of the hydroxyl group followed by hydrolysis (96 %) of the benzoate, hydrogenation (93 %) and PCC oxidation afforded **8**.

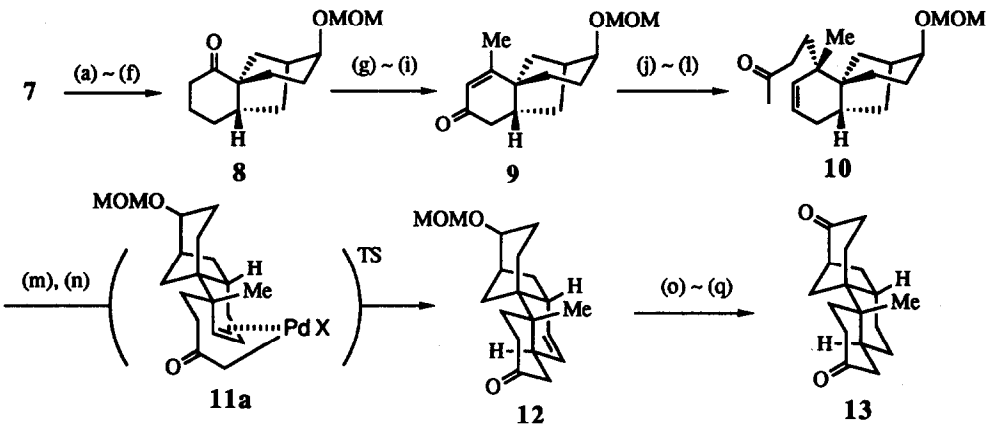
With convenient access to **8** secure, we then examined the stereoselective alkylation of the carbonyl containing ring. The ketone **8** was subjected to α,β-dehydrogenation[14] and methylation (78 %) followed by oxidation of the resulting allylic alcohol with PCC to furnish **9** (89 %). **9** was reduced with DIBAH (α–H:β-H=26:1) (88 %) to give the corresponding hydroxy product.[15] After etherification of the resulting alcohol (91 %), the Claisen rearrangement of the vinyl ether was conducted in toluene at 220 °C (91 %). Chain extension was next accomplished by sequential Wittig-like olefination[16] and hydrolysis.

With the efficient synthesis of **10** realized, the stage was now set for the completion of the synthesis. Upon treatment of the silyl enol ether of **10** with $Pd(OAc)_2$ in MeCN, the desired ketone **12** was produced in 56 % yield, presumably through the intermediacy of the alkylpalladium(II) complex **11a**.[6,17]

Finally, successive hydrogenation, deprotection and PCC oxidation provided the dione **13**, which displayed spectral properties identical with those reported by Piers and co-workers in a total synthesis of stemodin (**1**),[18] thus completing a formal synthesis of the latter.

In conclusion, a new, highly diastereocontrolled approach for the synthesis of stemodin (**1**) has been developed. Our methodology based on intramolecular Diels-Alder reaction and Pd^{2+}-promoted cyclization should prove an efficient tool in the syntheses of other complex diterpene systems, such as stemodinone[1] and maritimol.[19]

Scheme II



(a) $(Imid)_2C{=}S$, DMAP, CH_2Cl_2, (b) $^nBu_3SnH$, AIBN, C_6H_6, reflux, (c) MOMCl, $^iPr_2NEt$, $ClCH_2CH_2Cl$, (d) $LiOH{\cdot}H_2O$, aq. MeOH, (e) H_2, 10% Pd-C, EtOAc, (f) PCC, NaOAc, CH_2CH_2, (g) LDA, THF, PhSeBr ; 30% H_2O_2, (h) MeLi, n-hexane, (i) PCC, NaOAc,CH_2Cl_2, (j) DIBAH, CH_2Cl_2, -78 °C, (k) $CH_2{=}CHOEt$, $Hg(OAc)_2$, reflux ; 220 °C, toluene, (l) $Ph_2P(O)CH(OMe)Me$, LDA, THF ; 2.5% $HClO_4$, THF, (m) LDA, THF ; TMSCl, (n) $Pd(OAc)_2$, MeCN, r.t. → 45 °C, (o) H_2, 10% Pd-C, EtOAc, (p) aq. AcOH, 60 °C, (q) PCC, CH_2Cl_2

Acknowledgment. We are grateful to Prof. E. Piers for providing us with the spectral data of one of the intermediates in his stemodin synthesis.

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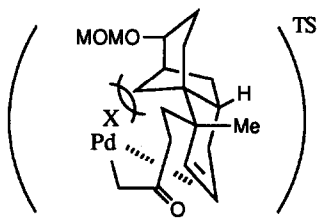
(17) (a) Davis, G. D. Jr. "Advances in Metal-Organic Chemistry" 1991, **2**, 59. (b) The steric congestion in the transition state **11b** makes it less favorable than the alternative transition state **11a** which gives rise to the desired product **12**.



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(Received in Japan 11 June 1993)