Tetrahedron Letters, Vol. 34, No. 38, pp. 6099-6102, 1993
Printed in Great Britain

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

Pd^{2+}-Promoted Cyclization in Linear Triquinane Synthesis Total Synthesis of (±)-Hirsutene

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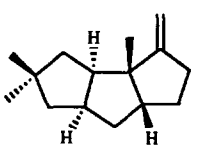
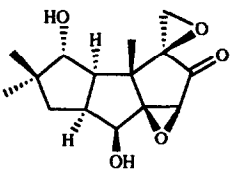
abstract: A sequence leading from *trans*-6-methyl-3-cyclohexenecarboxylic acid (3) to the *cis, anti, cis* - tricyclopentane ring system of the hirsutanes is described in which the key step utilizes an acid catalyzed intramolecular conjugate addition (5→**6a**) and a Pd^{2+}-promoted highly stereocontrolled cyclization (7→**8**).

Hirsutene (**1**)[1] and its more highly oxidized congener coriolin (**2**)[2] were isolated from Basidomycete *Coriolus consors*. The antibiotic and antitumor activities[3] of several members of the class have prompted widespread efforts at their synthesis.[4] There remains, however, a conspicuous need of general methods to prepare both simple and complex congeners and flexible ones to prepare topographical relatives.



hirsutene (**1**)



coriolin (**2**)

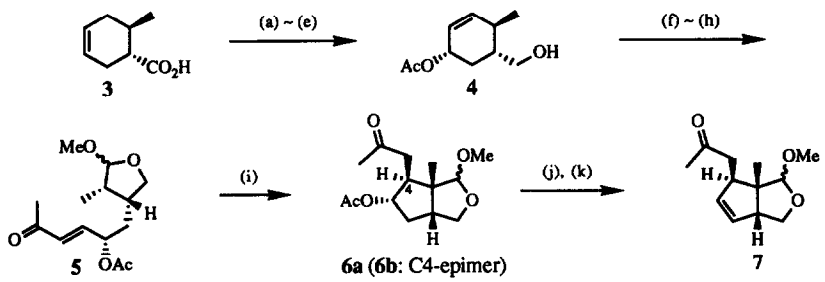
We herein embark upon a program to develop a unified strategy for the synthesis of linear condensed cyclopentanoids employing an acid catalyzed intramolecular conjugate addition and a Pd^{2+}-promoted cyclization as the key steps.

Conversion of the acid **3** into the functionalized cyclopenta[*c*]furan **7** was achieved via the reaction sequence summarized in Scheme I. A readily available **3**[5] was transformed to the alcohol **4** in the usual manner (1. iodolactonization, 2. elimination, 3. reduction, 4. protection, 5. acetylation,[6] 6. deprotection, 47% overall yield), which upon ozonolysis, Wittig reaction, and acetalization (69% from **4**) afforded **5**.

In order to construct the bicyclic compound **6a** diastereoselectively, the acid catalyzed conjugate addition[7] with TsOH in CH_2Cl_2 at 25 °C for 10 h was attemped, proceeding nicely to provide the ketone **6a**, together with its C4-epimer **6b** in a ratio of 10:1 (95%).[8] After hydrolysis (96%) of the above mixture, the corresponding alcohols were on the action of *o*-nitrophenyl selenocyanate and tri-n-butylphosphine,[9] converted into the selenide, oxidation of which with 30% hydrogen peroxide gave the olefin **7** (66%), along with recovered **6b**.

With convenient access to 7 secure, we then examined on the stereoselective Pd^{2+}-promoted cyclization for the construction of the third ring. Completion of the synthesis of (±)-**1** was carried out as summarized in Scheme II.

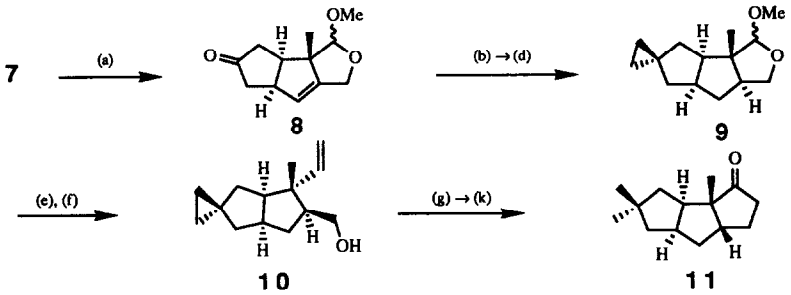
Scheme I



(a) I_2, KI, $NaHCO_3$, CH_2Cl_2-H_2O(1:1), 0 °C; DBU, THF, reflux, (b) LAH, THF, (c) TBSCl, imidazole, DMF, (d) Ac_2O, Py, DMAP, (e) $^nBu_4NF$, THF, (f) O_3, MeOH, -78 °C; Me_2S, (g) $Ph_3PCHCOMe$, $CHCl_3$, (h) MeOH, PPTS, 50 °C, (i) TsOH, CH_2Cl_2, (j) LiOH, MeOH-H_2O (3:1), 0 °C, (k) *o*-$NO_2PhSeCN$, $^nBu_3P$, THF; 30% H_2O_2, THF, 0 °C → r.t.

Upon treatment of the silyl enol ether of **7** with $Pd(OAc)_2$ in MeCN-CH_2Cl_2, the desired ketone **8** was produced in 99% yield, presumably through the intermediacy of the oxo-π-allylpalladium complex.[10] Results of nuclear Overhauser experiments confirm the assigned structrue for the ketone **8**.[11] The overall conversion of **3** into **8** was highly stereoselective and produced a functionalized tricycle in which the three contiguous quaternary stereogenic centers required for the eventual synthesis of (±)-**1** had been installed cleanly and efficiently. With the efficient synthesis of the highly functionalized tricyclic ketone **8** realized, the stage was now set for the completion of the synthesis. Catalytic hydrogenation of **8** in the presence of 10% palladium-charcoal led quantitatively to the corresponding ketone, which was subjected to Wittig olefination (57%) followed by cyclopropanation[12] of the resulting olefin with CH_2I_2 and Et_2Zn to furnish **9** (87%). The ring opening of **9** was next accomplished by sequential hydrolysis (79%) and Wittig reaction (77%) to give rise to the alcohol **10**.

Scheme II



(a) LDA, THF, -78 °C; TMSCl; $Pd(OAc)_2$, MeCN-CH_2Cl_2, (b) H_2, 10% Pd-C, EtOAc, (c) $Ph_3P^+MeBr^-$, ^nBuLi, DME, reflux, (d) CH_2I_2, Et_2Zn, C_6H_6, (e) aq. $HClO_4$, acetone, (f) $Ph_3P^+MeBr^-$, ^nBuLi, DME, reflux, (g) PCC, NaOAc, CH_2Cl_2, (h) $PdCl_2$, CuCl, O_2, DMF-H_2O, (i) $^nBu_4N^+OH^-$, THF-Et_2O-5% KOH (8:8:11), reflux, (j) H_2, PtO_2, NaOAc, AcOH, (k) PCC, NaOAc, CH_2Cl_2.

Finally, successive PCC oxidation, Wacker oxidation, aldol condensation[13] with epimerization, hydrogenation (84% from **10**)[14] and PCC oxidation (74%) provided the ketone **11**, displayed spectral properties identical with those reported[15] in a total synthesis of hirsutene (**1**), thus completing a formal synthesis of the latter.

In conclusion, a new, highly diastereocontrolled approach for the synthesis of hirsutene (**1**) has been developed. Our methodology based on acid catalyzed conjugate addition and Pd^{2+}-promoted cyclization should prove an efficient tool in the synthesis of other complex linear triquinane sesquiterpene systems, such as coriolin and hirsutic acid.[16]

Acknowledgement: We are grateful to Dr. Daniel D. Sternbach for providing us with the spectral data of one of the intermediates in his hirsutene synthesis.

References and Notes

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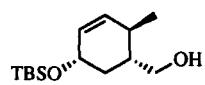
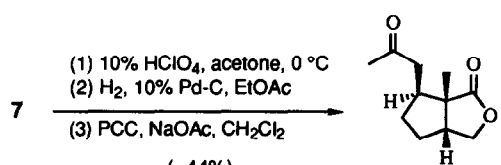


12

(7) Stork, G.; Atwal, K. S. *Tetrahedron Lett.* 1983, **24**, 3819-3822.

(8) Although the stereochemical assignment of **6a**, **6b** and **7** was not possible at this monent, successful elaboration of the olefin **7** to the known lactone **13**[7] definitely confirmed their stereochemistries as shown below.



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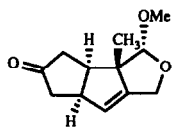
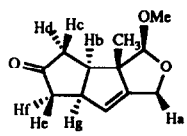
(11) Flash column chromatography on silica gel (4:1 hexane-EtOAc) provided two fractions. The first fraction gave **8a** (minor epimer); IR ($CHCl_3$): 1730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): d 1.02 (3H, s), 2.07 (1H, ddd, *J*=19.5, 9.3 and 1.5), 2.35 (1H, ddd, *J*=19.5, 9.8, and 1.5), 2.45 (1H, br d, *J*=19.0), 2.54 (1H, br dd, *J*=19.0 and 9.8), 3.29-3.37 (1H, m), 3.61-3.70 (1H, m), 4.26-4.34 (2H, m), 5.66-5.69 (1H, m). The second fraction gave **8b** (major epimer); IR ($CHCl_3$): 1730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): d 0.98 (3H, s), 2.08 (1H, ddd, *J*=19.2, 8.9 and 1.0), 2.37 (1H, ddd, *J*=19.2, 9.8 and 1.0), 2.49 (1H, br d, *J*=19.2), 2.53 (1H, br dd, *J*=19.2 and 10.0), 2.89 (1H, ddd, *J*=10.0, 8.9 and 1.0), 3.57-3.65 (1H, m), 4.28 (1H, br d, *J*=12.0), 4.46 (1H, ddd, *J*=12.0, 1.8 and 1.2), 5.63-5.66 (1H, m).



8a



8b

(NOE)

CH_3 ⟷ Hc (10.0%)

CH_3 ⟷ He (4.5%)

CH_3 ⟷ Ha (5.4%)

Hg ⟷ Hd (23.0%)

Hg ⟷ Hb (6.9%)

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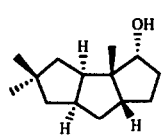
As expected, the over-reduction diastereoselectively occurred at this point, giving the alcohol **14** as a sole product. The stereochemistry of **14** was established by comparison of its ^1H NMR (500 MHz) spectrum with that reported[17] in the literature.



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^1H NMR (500 MHz, $CDCl_3$): δ 0.96 (3H, s), 0.97 (3H, s), 1.06 (3H, s), 1.29-1.52 (6H, m), 1.59-1.77 (4H, m), 1.92-2.01 (1H, m), 2.05-2.11 (1H, m), 2.53-2.66 (2H, m), 3.78 (1H, dd, J=6.7 and 6.7).

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(Received in Japan 31 May 1993; accepted 16 July 1993)