Pergamon

Tetrahedron Letters 40 (1999) 5377–5378

TETRAHEDRON LETTERS

Enantioselective Syntheses of (-)-7-Oxo-kolavenic Acid and (-)-Methyl Solidagonate from (-)-Verbenone

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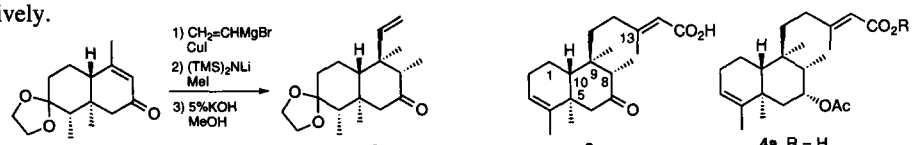
Received 20 April 1999; revised 19 May 1999; accepted 21 May 1999

Abstract: The first enantioselective synthesis of the title *neo-trans*-clerodanes **3** and **4b** from (-)-verbenone **5** has been accomplished using the ene reaction and stereoselective conjugate addition reaction to the enone **13** as the key step.

Keywords: natural products, asymmetric synthesis, stereocontrol, ene reactions

Since the important characteristics of clerodane diterpenes are not only the unique biological activity such as insect antifeedant, but also a contiguously arranged four-chiral center, C(5)-C(10)-C(9)-C(8) in the stereostructure,[1] synthetic efforts toward clerodane natural products have been focused on realization of this characteristic carbon-carbon framework in a stereocontrolled fashion.[1b] We have recently established an efficient construction of this carbon-carbon arrangement as a model: stereoselective conjugate addition reaction of *trans*-octalone **1** with a vinyl Grignard reagent followed by kinetically controlled methylation and base-induced epimerization to give the thermodynamically stable decalone **2** which possesses the same stereochemistry as those of *neo-trans*-clerodanes (Scheme 1).[2] In an application of this methodology, we show, starting with acetoxy ketone **6**, the first enantioselective syntheses of (-)-(5*R*,8*S*,9*R*,10*R*)-7-oxo-cleroda-3,13*E*-dien-15-oic acid (7-oxo-kolavenic acid) **3** and (-)-solidagonic acid **4a** as its methyl ester **4b**, isolated as a minor component from an extract of the aerial part of *Platychaete aucheri* [3] and from the root of *Solidago altissima* L.,[4] respectively.



Scheme 1

Stereoselective reduction of the acetoxy ketone **6**, which has been prepared from (-)-verbenone **5** (≥97% ee) in 7 steps and 36% overall yield,[2] with lithium tri-*tert*-butoxyaluminohydride provided alcohol **7** by exclusive attack of the hydride from the less-hindered β side (Scheme 2). Upon treatment with $POCl_3$ in pyridine, dehydration of **7** proceeded smoothly to afford diene **8**, whose hydrolysis followed by Swern oxidation of the resulting alcohol **9** gave aldehyde **10**. Stereoselective ene reaction of **10** with Et_2AlCl proceeded cleanly to give *trans*-octalol **11** with an axially oriented hydroxy group, as can be assumed by the well-documented reaction mechanism.[5] Swern oxidation of **11** produced a mixture (a 1:4 ratio) of deconjugate enone **12** and conjugate enone **13**. Upon treatment with DBU, the former was smoothly isomerized to the latter in quantitative yield. Finally, the compound **13** (98.9% ee) was prepared from **6** in 7 steps and more than 50 % overall yield.

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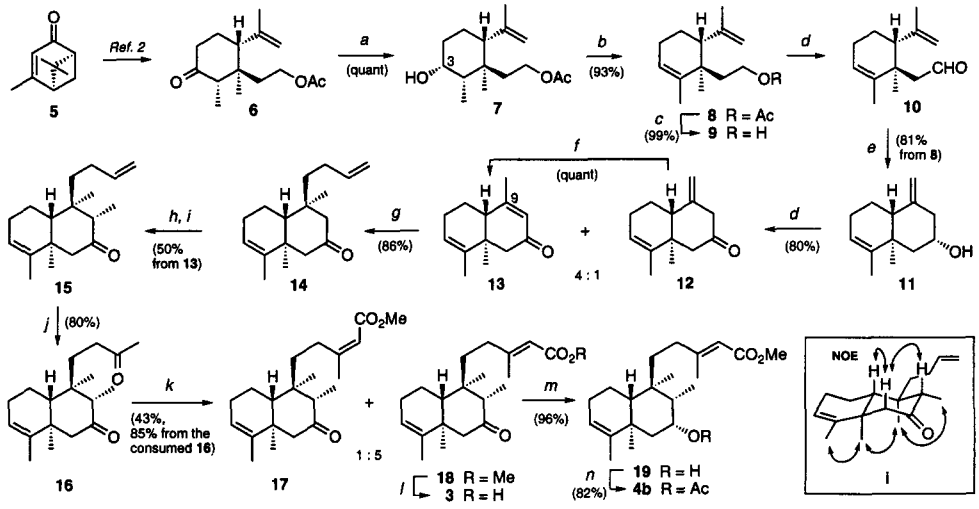
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01030-8

Installation of a homoallyl group at the C(9) position in **13** was carried out next; the stereoselective conjugate addition reaction of **13** successfully proceeded upon treatment with a homoallylcopper-BF_3 reagent to give the adduct **14** in 86% yield.[6] Methylation of **14** followed by epimerization of the newly-formed methyl group with a base provided the thermodynamically stable octalone **15**[7] in ca. 50% overall yield. The stereochemistry of **15** was confirmed as depicted in **i** by the NOE correlations. Palladium-catalyzed oxidation of the terminal olefin in **15** provided diketone **16**. Construction of an α,β-unsaturated ester unit in the side chain was accomplished by treating **16** with the sodium salt of methyl dimethoxyphosphonoacetate in THF to give a mixture (a 5:1 ratio) of the (*E*)-unsaturated ester **18**, $[\alpha]^{25}_D$ -96.6 ($CHCl_3$), and the (*Z*)-isomer **17**. It is worth mentioning that, in this Horner-Wadsworth-Emmons condensation, the ring carbonyl group in **16** was sterically hindered, so that upon exposure to a large excess of the phosphonate reagent, the condensation reaction occurred regioselectively at the ketone in the side chain to produce only a mixture of **17** and **18**, together with unchanged **16**. Hydrolysis of **18** provided the target compound **3** as an oil, $[\alpha]^{19}_D$ -95.2 ($CHCl_3$). The ^1H NMR (400 MHz) spectral data of synthetic **3** and **18** were indistinguishable from those of the natural **3** and its methyl ester **18**,[3] respectively. Finally, stereoselective reduction of the ketone in **18** followed by acetylation of the resulting alcohol **19** provided methyl solidagonate **4b**, $[\alpha]^{19}_D$ -83.4 (95% EtOH) {lit.[4] $[\alpha]^{14}_D$ -98.8 (95% EtOH)}, the spectral data of which were identical with those for the methyl ester of the natural isolate.[4]



Scheme 2. Reagents and conditions *a*, LiAlH(O*tert*-Bu)$_3$, THF; *b*, $POCl_3$, Py; *c*, K_2CO_3, MeOH;*d*, DMSO, $(COCl)_2$, CH_2Cl_2 then Et_3N; *e*, Et_2AlCl, CH_2Cl_2;*f*, DBU, CH_2Cl_2; *g*, CH_2=$CHCH_2CH_2MgBr$, BF_3·OEt_2, CuI, THF; *h*, LHMDS, MeI, THF; *i*, 5% KOH, MeOH; *j*, O_2, $PdCl_2$, CuCl, DMF, H_2O; *k*, $(MeO)_2POCH_2CO_2Me$, NaH, THF; *l*, KOH, MeOH, H_2O; *m*, $NaBH_4$, MeOH; *n*, Ac_2O, DMAP, Py.

References and Notes

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5. Snider, B. B. *The Prins and Carbonyl Ene Reactions in Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds., Pergamon Press, 1991,Vol. 2, pp. 527-561.
6. The reaction in the absence of Lewis acid was very sluggish, and after 10 h, **13** was mostly recovered unchanged.
7. ^1H NMR(400 MHz) 0.72 (3H, s), 0.94 (3H, d, *J* 6.6), 0.98 (3H, s), 1.35 (1H, m), 1.51-1.68 (4H, m), 1.57 (3H, s), 2.00 (1H, dd, *J* 10.5, 1.9), 2.02 (1H, m), 2.12 (2H, m), 2.29 and 2.46 (1H, d, *J* 11.7 each), 2.59 (1H, q, *J* 6.6), 4.96 (1H, d, *J* 11.0), 5.03 (1H, d, *J* 17.0), 5.27 (1H, s), 5.81 (1H, ddt, *J* 17.0, 11.0, 6.4)