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First enantioselective synthesis and determination of the absolute configuration of natural (+)-dehydro-β-monocyclonerolidol

Elie Palombo, Gérard Audran and Honoré Monti*

Laboratoire de Réactivité Organique Sélective, UMR 6516 (case 551), Faculté des Sciences et Techniques de St Jérôme, Avenue Escadrille Normandie, Niemen, 13397 Marseille Cedex 20, France

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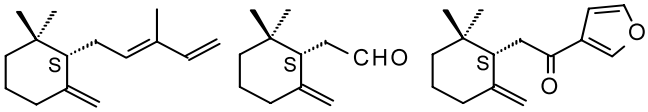
Abstract—The enantioselective synthesis and determination of the absolute configuration of (+)-dehydro-β-monocyclonerolidol, a natural product isolated from the liverwort *P. subobtusa*, has been achieved starting from (+)-karahana lactone as an enantiopure building block. Furthermore, the methodology applied provided a new approach towards the known (+)-γ-cyclohomocitral, a key intermediate in the sequence, and natural (+)-pallescensone.

In 1996, Asakawa et al.[1] isolated the monocyclofarnesane-type sesquiterpenoid (+)-**1** (Fig. 1) from the non-pungent group of liverwort *Porella subobtusa*. They characterized its structure as dehydro-β-monocyclonerolidol by extensive NMR techniques except for the absolute configuration which remained unknown.

In this letter we report the first enantioselective synthesis of (+)-**1** based on an original approach and starting from an enantiopure building block for the introduction and determination of the absolute configuration. The methodology used also allowed the synthesis of the known γ-cyclohomocitral,[2] (+)-**3**, as a key intermediate for the target molecule (+)-**1**, and of natural pallescensone,[3] (+)-**4** (Fig. 1). Our synthetic plan is outlined in Scheme 1.



(+)-**1** (+)-**3** (+)-**4**

Figure 1. Natural (+)-dehydro-β-monocyclonerolidol, (+)-**1**, is represented with the absolute configuration as determined in this work.

We recently reported[4] the synthesis of the required karahana lactone (+)-**2** [(1*R*,5*S*)-8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one] and demonstrated the utility of this enantiopure building block (or its enantiomer) in the synthesis of natural products.[5,6] Reduction of (+)-**2** with diisobutylaluminium hydride (DIBAL) as previously described,[5] gave a mixture of diastereomeric lactols **5** (and the opened aldehydic form) in 95% yield.[7] Exposure of the mixture of crude products **5** to the α-methoxy substituted ylid obtained by reacting methoxymethyltriphenyl-phosphonium chloride[8] with *n*-butyllithium in THF afforded **6** as a mixture of stereomers in 82% yield.

Barton–McCombie deoxygenation[9] of **6** was achieved via the corresponding xanthate, which was reduced smoothly with tri-*n*-butyltin hydride to provide **7** in an overall yield of 90% for the two steps. Subsequent hydrolysis at 0°C with 1 M HCl (THF/H_2O) gave γ-cyclohomocitral (+)-**3**, $[\alpha]_D^{25}$ +31 ($CHCl_3$)/lit.[2] $[\alpha]_D^{20}$ +29.0 (CH_2Cl_2), in 79% yield.[7] The chiral information was encoded in this key intermediate, the absolute configuration of which is (*S*). The aldehyde (*S*)-**3** was subjected to a Wittig olefination with the commercially available 2-(triphenyl-phosphoranylidene) propionaldehyde to stereoselectively form the carbon chain extended *E*-α,β-unsaturated aldehyde (+)-**9** as a single stereomer in 90% yield.[7]

Finally, a subsequent methylenation of (+)-**9** with the salt-free Wittig reagent prepared from methyltriphenyl-phosphonium iodide and *tert*-BuOK yielded the target molecule (+)-**1** in 92% yield. The spectroscopic data (^{1}H

* Corresponding author. Tel./fax: +33-4-91288862; e-mail: honore.monti@univ.u-3mrs.fr

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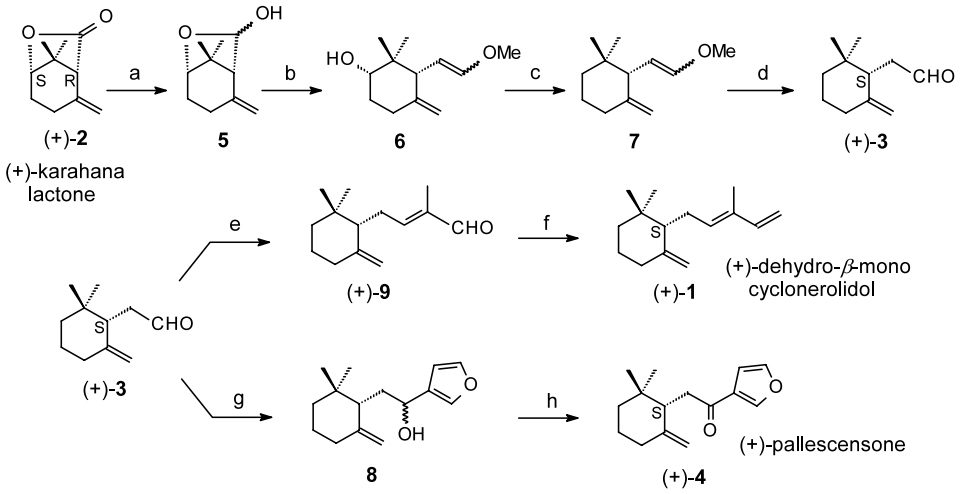

Scheme 1. *Reagents and conditions*. (a) DIBAL, toluene, −70°C, 95%; (b) $Ph_3P^+CH_2OMeCl^-$, *n*-BuLi, THF, rt, 82%; (c) i. NaH, CS_2, MeI, rt, THF; ii. $HSnBu_3$, cat. AIBN, toluene, reflux, 90% (two steps); (d) 1 M HCl/THF: 1/2, rt, THF, 79%; (e) $Ph_3P{=}C(CH_3)CHO$, toluene, reflux, 90%; (f) $Ph_3P^+MeI^-$, *tert*-BuOK, toluene, rt, 92%; (g) 3-bromofuran, *n*-BuLi, THF, −78°C, 80%; (h) NMO, cat. $(n\text{-Pr})_4NRuO_4$, 4 Å MS, CH_2Cl_2, rt, 70%.

and ^{13}C NMR) of synthetic (+)-**1** matched those reported for natural **1**[1,7] and the specific rotation was comparable in magnitude and the same in sign, $[\alpha]_D^{25}$ +10 ($CHCl_3$)/lit.[1] $[\alpha]_D^{20}$ +9.5 ($CDCl_3$), indicating the synthesis of the natural enantiomer. The (*S*)-configuration was therefore assigned to natural dehydro-β-monocyclonerolidol (+)-**1**.

Additionally, (+)-γ-cyclohomocitral, (*S*)-**3**, was converted into (+)-pallescensone, (*S*)-**4**, in two steps according to published procedures.[2,10] Reaction with a solution of 3-furyllithium in THF afforded the diastereomeric alcohols **8** in 80% yield, and they were smoothly oxidized with tetrapropylammonium perruthenate (TPAP)[11] to give crystalline pallescensone (mp 54°C) in 70% yield. The crystalline nature of pallescensone has never been reported.

In conclusion, an asymmetric synthesis of a new monocyclic sesquiterpenoid isolated from *P. subobtusa* has been achieved for the first time, and the absolute configuration has been determined. The merits of this approach are high-yielding reaction steps and secured absolute configuration.

References

1. Nagashima, F.; Izumo, H.; Ishimaru, A.; Momasaki, S.; Toyota, M.; Hashimoto, T.; Asakawa, Y. *Phytochemistry* **1996**, *43*, 1285–1291.
2. Vidari, G.; Lanfranchi, G.; Masciaga, F.; Moriggi, J.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 3009–3020.
3. Cambie, R. C.; Bergquist, P. A.; Karuso, P. *J. Nat. Prod.* **1987**, *50*, 948–949.
4. Galano, J.-M.; Audran, G.; Monti, H. *Tetrahedron* **2000**, *56*, 7477–7481.
5. Audran, G.; Galano, J.-M.; Monti, H. *Eur. J. Org. Chem.* **2001**, 2293–2296.
6. Audran, G.; Uttaro, J.-P.; Monti, H. *Synlett* **2002**, 1261–1264.
7. All new compounds were fully characterized spectroscopically and had satisfactory microanalyses. **Selected data**: Compound (+)-**3**, $[\alpha]_D^{25}$ +31 (*c* 1.0, $CHCl_3$), lit.[2] $[\alpha]_D^{20}$ +29.0 (*c* 0.35, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 9.62 (t, 1H, $J=2.3$ Hz), 4.79 (s, 1H), 4.50 (s, 1H), 2.52–2.40 (m, 3H), 2.18 (dt, 1H, $J=13.2$, 5.8 Hz), 2.03 (ddd, 1H, $J=13.2$, 8.0, 5.5 Hz), 1.65–1.22 (m, 4H), 0.96 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 148.5, 109.2, 47.8, 41.5, 38.5, 34.9, 34.4, 28.8, 23.5, 23.4. Anal. calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.31; H, 10.94. Compound (+)-**9**, $[\alpha]_D^{25}$ +20 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.32 (s, 1H), 6.40 (tq, 1H, $J=7.5$, 1.2 Hz), 4.77 (br s, 1H), 4.47 (br s, 1H), 2.55–2.34 (m, 2H), 2.15–1.90 (m, 3H), 1.72 (d, 3H, $J=1.0$ Hz), 1.58–1.43 (m, 3H), 1.34–1.23 (m, 1H), 0.96 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 155.3, 148.3, 138.9, 109.5, 53.3, 37.3, 35.1, 33.4, 28.6, 26.4, 24.8, 23.5, 9.27. Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.77; H, 10.72. Compound (+)-**1**, $[\alpha]_D^{25}$ +10 (*c* 2.0, $CHCl_3$), lit.[1] $[\alpha]_D^{20}$ +9.5 (*c* 10.1, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.35 (dd, 1H, $J=17.4$, 10.8 Hz), 5.40 (t, 1H, $J=6.8$ Hz), 5.03 (d, 1H, $J=17.3$ Hz), 4.88 (d, 1H, $J=10.8$ Hz), 4.75 (s, 1H), 4.49 (d, 1H, $J=1.9$ Hz), 2.35 (ddd, 1H, $J=15.5$, 6.4, 4.0 Hz), 1.97 (m, 1H), 1.82 (dd, 1H, $J=11.1$, 4.0 Hz), 1.73 (s, 3H), 1.55–1.42 (m, 3H), 1.36–1.22 (m, 1H), 0.95 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 141.7, 133.4×2, 109.9, 109.0, 54.0, 37.5, 35.1, 33.6, 28.8, 25.5, 24.9, 23.7, 11.8. Anal. calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.94; H, 11.87.
8. Soderquist, J. A.; Ramos-Veguilla, J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, pp. 3363–3365.
9. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin 1* **1975**, 1574–1585.
10. Baker, R.; Cottrell, J. F.; Ravenscroft, P. D.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2463–2468.
11. Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13–19.