

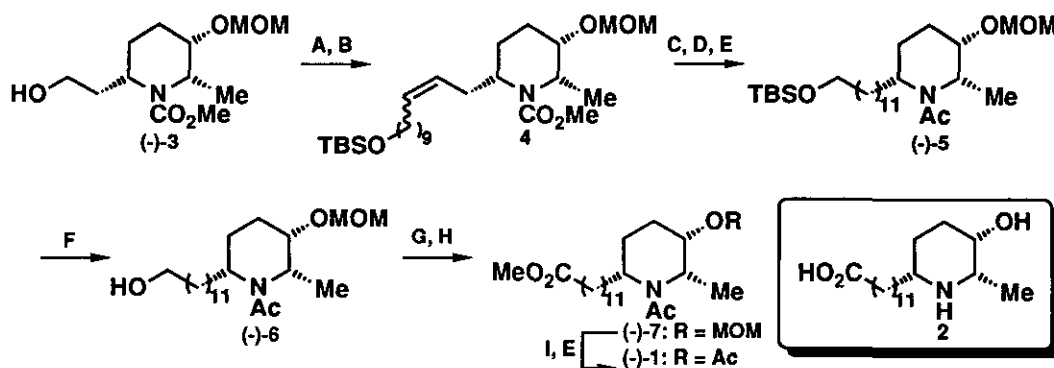
ASYMMETRIC SYNTHESIS OF METHYL *N*, *O*-DIACETYL-SPICIGERINATE

Takefumi Momose* and Naoki Toyooka

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Abstract - The first asymmetric synthesis of methyl *N*, *O*-diacetylspicigerinate (**1**) has been achieved, and the absolute configuration of the parent alkaloid (**2**) was determined to be 2*S*, 3*S*, 6*R*.

Spicigerine (**2**), isolated from the leaves of *Prosopis spicigera*,¹ is one of the piperidin-3-ol alkaloid and displays interesting biological activities.² Although the gross structure of **2** has been proposed as depicted by spectroscopic studies,¹ the absolute configuration has not been determined. In the preceding paper, we have exhibited a design for the asymmetric synthesis of the piperidin-3-ol alkaloids (-)-cassine and (+)-spectaline starting with both enantiomers of the key piperidine (**3**).³ We have examined the application of the design to the first asymmetric synthesis of methyl *N*, *O*-diacetylspicigerinate (**1**)⁴ and the determination of the absolute configuration of **1**. The carbon-chain elongation of (-)-**3** was achieved in two steps to give the olefin (**4**) in 74% yield. Hydrogenation of **4**⁵ followed by interconversion of the *N*-acyl afforded the amide [(-)-**5**] in 73% overall yield. Treatment of (-)-**5** with TBAF gave the alcohol [(-)-**6**] in 85% yield. Oxidation of (-)-**6** and esterification of the resulting acid with diazomethane gave the ester [(-)-**7**] in 63% overall yield. Finally, conversion of the methoxymethyl in (-)-**7** into the acetyl furnished the desired ester [(-)-**1**]⁶ {[α]_D²⁶ -17.2 (*c* 1.10, CDCl₃), lit.,¹ [α]_D²⁵ -6.3 (*c* 0.63, CDCl₃)} in 92% yield.



Reagents and conditions: A Swern oxidn.; B TBSO(CH₂)₉CH=PPh₃, 0 °C~room temperature; C 5% Pd-C, H₂; D ⁿPrSLi, HMPA-THF, room temperature; E Ac₂O, Py; F TBAF, 0 °C~room temperature; G PDC, DMF; H CH₂N₂, CH₂Cl₂; I c. HCl, MeOH

Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

In conclusion, the absolute configuration of **2** was determined to be *2S, 3S, 6R*⁷ by the present asymmetric synthesis.

REFERENCES

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2. G. M. Strunz and J. A. Findlay, "The Alkaloids" ed. A. Brossi, Academic Press, New York, 1985, Vol. 26, ch. 3.
3. T. Momose and N. Toyooka, *Tetrahedron Lett.*, 1993, **34**, 5785.
4. In order to verify the structure assigned to spicigerine, the alkaloid was converted into (-)-**1** by Jewers *et al.* ¹H Nmr spectroscopic data for (-)-**1** has been reported; see reference 1.
5. Satisfactory analytical and spectral data were obtained for all new compounds.
6. The spectroscopic properties of (-)-**1** were as follows: Ir (neat) cm⁻¹: 2926 s, 2854, 1739 s, 1646 s, 1414, 1368, 1238 s; ¹H-nmr (500 MHz, CDCl₃) δ: 1.14 & 1.20 (3H, each d, each *J* = 7.1 Hz, due to rotamers), 1.25 (17H, br), 1.49 (1H, br), 1.57-1.86 (6H, br m), 2.03 & 2.06 (3H, each s, due to rotamers), 2.10 (3H, br s), 2.39 (2H, t, *J* = 7.2 Hz), 3.65 (3H, s), 3.70 (0.5H, br, due to rotamers), 4.21 (0.5H, quintet, *J* = 6.9 Hz, due to rotamers), 4.57 (0.5H, q-like, *J* = 7.5 Hz, due to rotamers), 4.77 (1H, m), 4.95 (0.5H, quintet, *J* = 7.0 Hz, due to rotamers); ¹³C-nmr (125 MHz, CDCl₃) δ: 14.29 & 15.12 (each CH₃, due to rotamers), 19.74 & 19.82 (each CH₂, due to rotamers), 21.14 (CH₃), 22.06 & 22.42 (each CH₃, due to rotamers), 24.91 (CH₂), 25.53 (CH₂), 26.21 (CH₂), 27.53 & 27.78 (each CH₂, due to rotamers), 29.10 (CH₂), 29.21 (CH₂), 29.38 (CH₂), 29.48 (CH₂), 29.53 (CH₂), 29.61 (CH₂), 34.07 & 34.54 (each CH₂, due to rotamers), 35.28 (CH₂), 45.38 & 47.19 (each CH, due to rotamers), 50.27 & 52.72 (each CH, due to rotamers), 51.42 (CH₃), 71.25 & 72.02 (each CH, due to rotamers), 170.07 (C), 170.23 (C), 174.30 (C); hrms: Calcd for C₂₃H₄₁NO₅, 411.2983; found, 411.2970.
7. Jewers *et al.* predicted that the absolute configuration of **1** is *2R, 3R, 6S* by comparison of the ORD of (-)-**2** with those of the related 3-piperidinol alkaloid cassine and a number of 2-alkylated piperidines.

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