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

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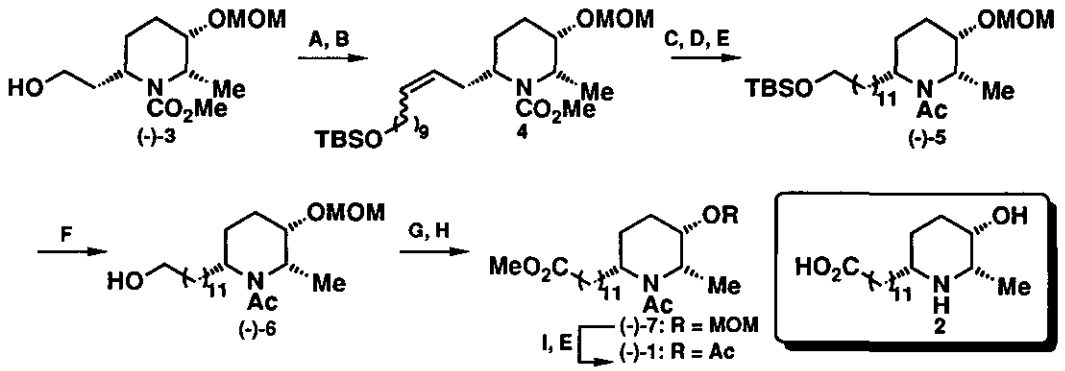
Abstract - The first asymmetric synthesis of methyl *N*, *O*-diacetylspicigerinate (**1**) has been achieved, and the absolute configuration of the parent alkaloid (**2**) was determined to be 2*S*, 3*S*, 6*R*.

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] {$[\alpha]_D^{26}$ -17.2 (*c* 1.10, $CDCl_3$), lit.,[1] $[\alpha]_D^{25}$ -6.3 (*c* 0.63, $CDCl_3$)} in 92% yield.



Reagents and conditions: **A** Swern oxidn.; **B** $TBSO(CH_2)_9CH{=}PPh_3$, 0 °C~room temperature; **C** 5% Pd-C, H_2; **D** ^nPrSLi, HMPA-THF, room temperature; **E** Ac_2O, Py; **F** TBAF, 0 °C~room temperature; **G** PDC, DMF; **H** CH_2N_2, CH_2Cl_2; **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 2*S*, 3*S*, 6*R*[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.
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4. In order to verify the structure assigned to spicigerine, the alkaloid was converted into (-)-**1** by Jewers *et al.* ^{1}H 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; ^{1}H-nmr (500 MHz, $CDCl_3$) 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); ^{13}C-nmr (125 MHz, $CDCl_3$) δ: 14.29 & 15.12 (each CH_3, due to rotamers), 19.74 & 19.82 (each CH_2, due to rotamers), 21.14 (CH_3), 22.06 & 22.42 (each CH_3, due to rotamers), 24.91 (CH_2), 25.53 (CH_2), 26.21 (CH_2), 27.53 & 27.78 (each CH_2, due to rotamers), 29.10 (CH_2), 29.21 (CH_2), 29.38 (CH_2), 29.48 (CH_2), 29.53 (CH_2), 29.61 (CH_2), 34.07 & 34.54 (each CH_2, due to rotamers), 35.28 (CH_2), 45.38 & 47.19 (each CH, due to rotamers), 50.27 & 52.72 (each CH, due to rotamers), 51.42 (CH_3), 71.25 & 72.02 (each CH, due to rotamers), 170.07 (C), 170.23 (C), 174.30 (C); hrms: Calcd for $C_{23}H_{41}NO_5$, 411.2983; found, 411.2970.
7. Jewers *et al.* predicted that the absolute configuration of **1** is 2*R*, 3*R*, 6*S* 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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