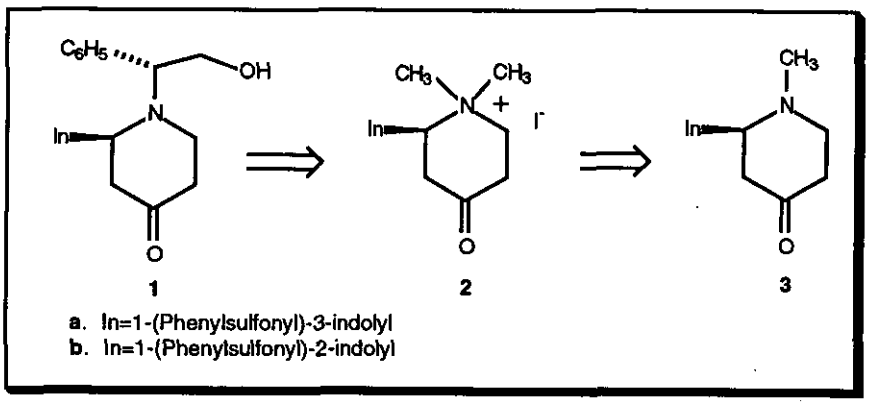
SYNTHESIS OF CHIRAL 2-ARYL-4-PIPERIDONES

Mario Rubiralta,* Anna Diez, Cristina Vila, Josep Castells, and Isabel López

Laboratory of Organic Chemistry, Faculty of Pharmacy,
University of Barcelona, 08028 Barcelona, Spain

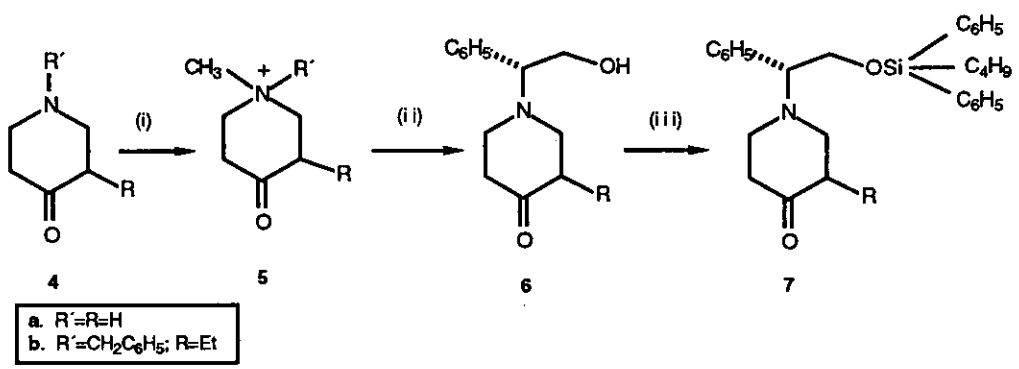
Abstract--The synthesis of chiral 2-(2-indolyl)- and 2-(3-indolyl)-4-piperidones by reaction of *N,N*-dimethyl-4-oxo-2-[1-(phenylsulfonyl)-indolyl]piperidinium iodide and (*R*)-(-)-phenylglycinol is reported.

Some years ago we developed an improved synthesis of 2-aryl-4-piperidones which has been applied to the synthesis of a large number of compounds related to natural products and pharmacologically active compounds.[1,2] However, until now there is no suitable way described to prepare chiral 2-aryl-4-piperidones, even if very recently, the synthesis of chiral 4-piperidones by the use of a rarely employed reaction between *N,N*-dimethyl-4-oxopiperidinium iodide and (*S*)-(-)-α-methylbenzylamine has been reported.[3] In this paper we describe the application of this methodology using (*R*)-(-)-phenylglycinol and 2-arylpiperidinium salts (**2**) to obtain chiral 2-[1-(phenylsulfonyl)-2-indolyl]- and 2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidones (**1a**) and (**1b**) (Scheme 1).



Scheme 1

We first treated piperidinium salts (**5**) with (*R*)-(-)-phenylglycinol and K_2CO_3 in ethanol obtaining the chiral piperidones (**6**) in reasonable yields.[4,5] Then, the hydroxy group was protected as a silyl ether (**7**).[6] It is worth mentioning that the quaternization reaction of **4b**[7] into **5b** only yielded the hydrate form of **5b**.[8,9] This fact was corroborated by the spectroscopic data. Thus, in the ir spectrum of **5b**.H_2O no absorption at 1705 cm^{-1} but an intense OH band were observed, and the ^{13}C nmr spectrum presented a typical chemical shift value of δ 95.5 for C-4. After heating **5b**.H_2O at 80°C under a 5 mmHg vacuum for 2 hours the dehydrated compound (**5b**) was obtained, which clearly showed the absorption at 1710 cm^{-1} in the ir spectrum and the signal at δ 208.5 in the ^{13}C nmr characteristic of the carbonyl function. Reaction of piridinium salt (**5b**) with (*R*)-(-)-phenylglycinol in the standard conditions yielded a 1:1 diastereomeric mixture of chiral 4-piperidones (**6b**)[10] in 40% yield, which was separated by flash chromatography and the isomers were identified by spectroscopic data. In particular, signals at δ 60.8 and 69.3 were observed for the hydroxyethyl chain in the ^{13}C nmr spectra of both compounds and significant differences were only observed for C-2 and

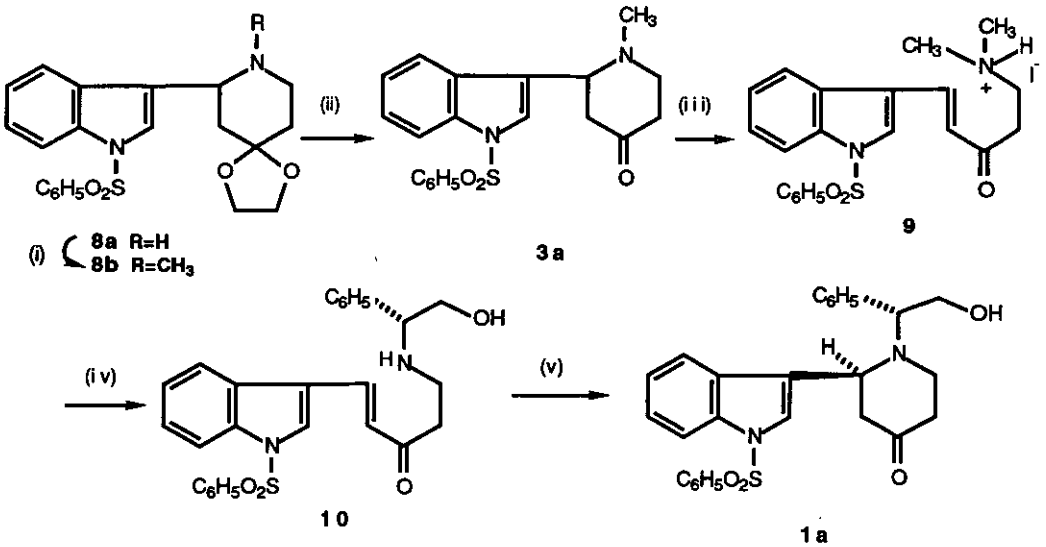


Reagents and Conditions: (i) CH_3I (5 eq.), acetone, room temperature (a: 98%, b: 79%). (ii) 1. (*R*)-(-)-phenylglycinol (1 eq.), K_2CO_3 (2 eq.), C_2H_5OH-H_2O, Δ; 2. slow addition of **5a** in CH_2Cl_2; 3. Δ, 3-5 h (a. 56%, b: 40%). (iii) TBDPSCl (1.2 eq., imidazole (2 eq.), CH_2Cl_2, Δ, 12 h (~95%).

Scheme 2

C-6 (56.0 and 47.8 for isomer ($\alpha R,3S$), and δ 51.3 and 52.4 for isomer ($\alpha R,3R$), respectively) indicating that the ethyl substituent adopts an equatorial orientation in the preferred ring conformation of each isomer.

In a further step, we prepared 2-indolyl-4-piperidone (**3a**) by methylation of piperidine (**8a**)[1] and hydrolisis of the resulting acetal (**8b**). Quaternization of piperidone (**3a**) with an excess of methyl iodide in acetone led to enone (**9**)[11] as the result of the piperidone ring fragmentation.[12,13] Formation of **9** was evidenced by the presence of two doublets (J=16 Hz) at δ 6.8 and 7.7 in the ^{1}H nmr spectrum corresponding to the *trans* olefin protons and by the ^{13}C nmr chemical shift at δ 199.5 for the carbonyl group. Formation of **9** as a hydroiodide was showed by subsequent liberation to the free amine (**9**) with an aqueous potassium carbonate solution. The most significant modification observed in the^{1}H nmr spectra was the shielding (Δδ 0.55) of the singlet corresponding to the *N*-methyl groups.



Reagents and Conditions: (i) CH_3I (1.5 eq.), acetone, room temperature, 5 h (91% yield). (ii) 4*N* HCl, CH_3OH, Δ, 10 h (96% yield). (iii) CH_3I (4 eq.), acetone, room temperature (65% yield). (iv) 1. (*R*)-(-) phenylglycinol (1 eq.), C_2H_5OH-H_2O, K_2CO_3; 2. **9** in CH_2Cl_2, slow addition, Δ, 5 h. v) EtOH, room temperature, overnight.

Scheme 3

The following treatment of **9** with (*R*)-(-)-phenylglycinol provided enone (**10**),[14] which furnished piperidone (**1a**)[15] by cyclization in ethanol. Compound (**1a**) showed to be a single diastereomer, in which the 2-aryl substituent is in an axial disposition (δ 4.55, doublet of doublets, *J*=7 and 5 Hz). It is worth noting that transformation of 4-ketopiperidinium salts such as **5** into **6** usually involves a three step mechanism: (i) opening of the piperidine ring by a Hofmann β-elimination promoted by the base; (ii) Michael addition of the chiral amine; and (iii) displacement of dimethylamine.[9,16,17] A similar mechanism could be expected in the transformation of **3a** into **1a**, but instead, enone (**10**) is isolated, which indicates that a substitution of the ammonium salt takes place before the Michael addition.

Finally, piperidone (**3b**), obtained from its corresponding acetal by hydrolisis,[18] was also quaternized with an excess of methyl iodide (Scheme 4). In a similar manner than in the previous case, enone (**11**)[19] was isolated, which was identified by its spectroscopic data. Reaction of **11** with (R)-(-)-phenylglycinol furnished enaminone (**12**), which was directly cyclized yielding satisfactorily the desired piperidone (**1b**).[20,22]

The formation of a single epimer in the case of 2-indolyl-4-piperidones (**1**) can be accounted for by considering an equilibrium between the open enones (**10** and **12**) and the cyclized structures, which leads to the exclusive formation of the thermodynamically most stable isomer.

ACKNOWLEDGEMENTS

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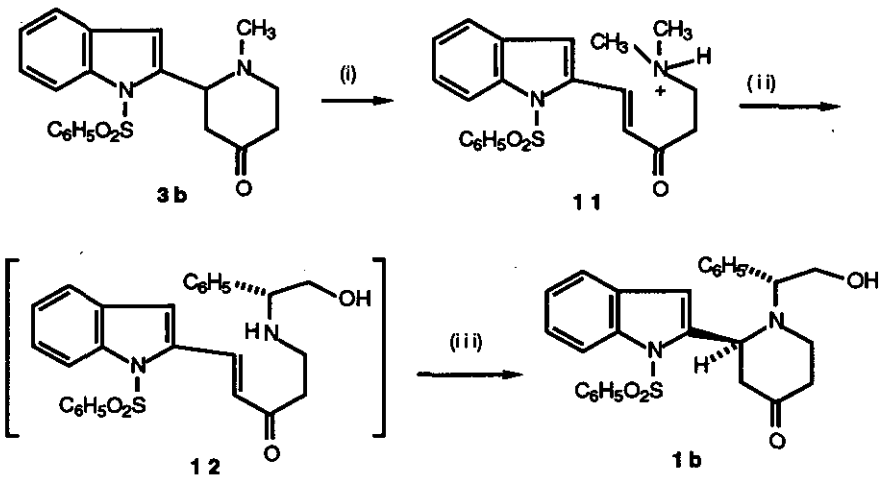

Reagents and Conditions: (i) CH_3I (4 eq.), acetone, room temperature (60%) (ii) 1. (*R*)-(-)-phenylglycinol, C_2H_5OH-H_2O, K_2CO_3, Δ; 2. **11** in CH_2Cl_2 is slowly added, Δ, 5 h (iii) C_2H_5OH, room temperature, overnight.

Scheme 4

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4. All new compounds were identified by their spectral data, optical rotation, and elemental analysis.
5. **6a**: $[\alpha]_D$ -19.3° (c=1, C_2H_5OH); ir ($CHCl_3$) 3456 (OH), 1716 (CO); ^1H nmr 2.50-2.60 (m, 2H, $COCH_2$), 2.68 (m, 2H, 2-Ha), 2.89 (m, 2H, 2-He), 3.70-4.10 (m, 3H, NCH

CH_2), 7.10-7.50 (m, 5H, ArH); ^{13}C nmr 41.5 (C-3), 48.5 (NCH_2), 60.9 ($HOCH_2$), 69.5 (NCH), 128.4, 128.6, 135.0, 208.4 (CO).

6. **7a:** $[\alpha]_D$ -6° (c=1, C_2H_5OH); ir ($CHCl_3$) 1712 (CO); ^1H nmr 1.10 (s, 9H, CH_3), 2.43 (t, *J*=6 Hz, 4H, $COCH_2$), 2.82 (t, *J*=6 Hz, 4H, NCH_2), 3.70 (t, *J*=6 Hz, 2H, NCH), 3.95 and 4.12 (2 dd, *J*=11, 6 Hz, 1H each, $SiOCH_2$), 7.10-7.80 (m, 15H); ^{13}C nmr 26.4 ($SiCH_3$), 41.2 ($SiCCH_3$), 41.5 (C-3), 50.7 (C-2), 66.0 ($SiOCH_2$), 70.1 (NCH), 121.7, 127.2, 127.5, 127.8, 129.6, 129.7, 133.4, 134.9, 135.7, 140.2, 210.3 (CO).
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10. **6b** (α***R***,3***S***)**: ir ($CHCl_3$) 3430 (OH), 1712 (CO); ^1H nmr 0.87 (t, *J*=7 H, 3H, CH_3), 1.25 (m, 1H, $CHCH_3$), 1.80 (m, 1H, $CHCH_3$), 3.72 (t, *J*=5 Hz, 1H, NCH), 3.85 (dd, *J*=10, 5 Hz, 1H, CHOH), 4.03 (dd, *J*=10, 5 Hz, 1H, CHOH), 7.1-7.5 (m, 5 H, ArH); ^{13}C nmr 11.4 (CH_3), 20.4 (CH_2), 40.8 (C-5), 47.8 (C-6), 51.6 (C-3), 56.0 (C-2), 60.8 (CH_2OH), 69.3 (NCH), 127.5, 128.2, 129.0, 134.8, 209.8 (CO).
11. **9**.hydroiodide: ir (KBr) 1645 (C=O); ^1H nmr 2.85 (s, 6H, $^+NCH_3$), 3.40-3.50 (m, 4H, CH_2CH_2), 6.85 (d, *J*=16 Hz, 1H, =CHCO), 7.65 (d, *J*=16 Hz, 1H, =CHIn), 7.00-8.00 (m, 10H); ^{13}C nmr 35.3 ($COCH_2$), 43.5 (NCH_3), 52.8 (NCH_2), 113.7, 121.0, 124.5, 124.9, 125.8, 127.0, 129.6, 130.1, 134.5, 136.2, 199.5 (CO). **9**: ^1H nmr 2.30 (s, 6H, NCH_3), 2.70 and 2.85 (2 t, *J*=7 Hz, 2H each, CH_2CH_2), 6.89 (d, *J*=16 Hz, 1H, =CHCO), 7.72 (d, *J*=16 Hz, 1H, =CHIn), 7.20-8.05 (m, 10H); ^{13}C nmr 39.0 ($COCH_2$), 45.3 (NCH_3), 54.2 (NCH_2), 113.8, 120.8, 124.3, 125.7, 126.3, 126.7, 128.8, 129.6, 133.7, 134.5, 199.2 (CO).
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14. **10**: $[\alpha]_D$ -21° (c=1, C_2H_5OH); ir ($CHCl_3$) 3550 (OH), 1670 (CO), 1604 (C=C); ^1H nmr 3.50-4.00 (m, 4H, CH_2CH_2), 3.60-3.80 (m, 2H, $HOCH_2$), 3.85 (dd, *J*=10, 4 Hz, 1H, NC*H*Ph), 6.80 (d, *J*=16 Hz, 1H, =CHCO), 7.70 (d, *J*=16 Hz, 1H, =CHIn), 7.10-8.00 (m, 15H); ^{13}C nmr 40.0 (CO*C*H2), 42.0 (NCH_2), 64.7 ($HOCH_2$), 65.9 (NCHPh), 113.8 (In-C7), 120.7 (In-C4), 124.7 (In-C5), 125.7 (In-C6), 125.9 (=CH), 126.9 and 127.3 (C_6H_5-*ortho*), 128.2 (C_6H_5-*ipso*), 129.2 and 129.6 (C_6H_5-*meta*), 134.3 and 134.4 (C_6H_5-*para*), 198.7 (C=O).

15. **1a**: $[\alpha]_D$ -3.0° (c=1, C_2H_5OH); ir ($CHCl_3$) 3500 (OH), 1715 (C=O); ^1H nmr 2.33 (td, *J*=11.5, 3 Hz, 1H, 5-Ha), 2.90 (dd, *J*=13, 10 Hz, 1H, 3-Ha), 3.00-3.14 (m, 1H), 3.30-3.41 (m, 1H), 3.35-3.60 (m, 2H), 6.98 (br s, 1H, In-2H), 7.10-8.20 (m, 14H); ^{13}C nmr 41.3 (C-5), 44.6 (C-3), 47.8 (C-6), 57.3 (C-2), 61.1 (CH_2OH), 63.2 (NCHPh), 114.4, 120.6, 123.8, 125.0, 125.7, 126.9, 128.5, 129.2, 129.5, 134.2, 207.2 (CO).

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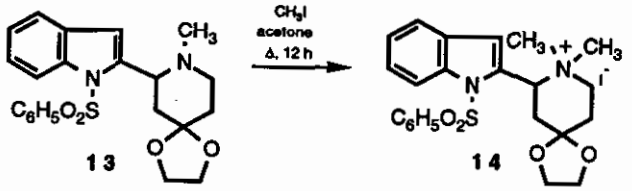
19. **11**: mp 184-186°C (acetone); ^1H nmr (200 MHz, $CDCl_3$-CD_3OD) 2.98 (s, 6H, NCH_3), 3.44 (br t, *J*=7 Hz, 2H, $COCH_2$), 3.88 (br t, *J*=7 Hz, 2H, NCH_2), 6.85 (d, *J*=16 Hz, 1H, =CH),7.20 (s, 1H, In-3H), 7.20-7.60 (m, 7H), 7.72 (d,*J*=7.5 Hz, 1H, In-7H), 8.20 (d, *J*=7.5 Hz, 1H, In-4H), 8.42 (d, *J*=16 Hz, 1H, =CH); ^{13}C nmr (CD_3OD) 34.2 ($COCH_2$), 42.2 (NCH_3), 52.1 (NCH_2), 113.7, 114.5, 121.5, 124.2, 125.8, 125.6, 126.3, 128.9, 132.9, 133.9, 196.1 (CO).

20. The acetal **13**,[18] precursor of 2-indolyl-4-piperidone (**3b**), was transformed into piperidinium salt (**14**),[21] in good yield, without formation of opened product.



21. **14**: ^{1}H nmr 1.55 (d, J=14 Hz, 1H, 3-He), 2.05 (d, J=14 Hz, 1H, 5-He), 2.40 (td, J=14, 4 Hz, 1H, 5-Ha), 3.13 (t, J= 13 Hz, 1H, 3-Ha), 3.31 (s, 3H, axial NCH_3), 3.42 (s, 3H, equatorial NCH_3), 3.65 (t, J=14 Hz, 1H, 6-Ha), 3.9-4.2 (m, 4H, OCH_2), 4.60 (d, J=14 Hz, 1H, 6-He), 5.80 (d, J=13 Hz, 1H, 2-Ha), 7.20-7.75 (m, 9H), 8.30 (d, J=7 Hz, 1H); ^{13}C nmr 30.1 (C-5), 37.1 (C-3), 43.4 (axial NCH_3), 54.2 (equatorial NCH_3), 63.5 (C-6), 64.9 and 65.4 (OCH_2), 65.6 (C-2), 103.9 (C-4), 116.1, 121.0, 122.8, 125.4, 125.8, 127.6, 128.8, 129.5, 135.1, 136.8, 138.2.

22. **1b**: Ir ($CHCl_3$) 3691 (OH), 1714 (CO); ^{1}H nmr 1.72 (br d, J= 13 Hz, 1H, 3Ha), 1.80-2.00 (m, 1H), 2.30-3.00 (m, 4H), 3.80-4.05 (m, 3H, $PhCHCH_2$), 6.80 (s, 1H, In-3H), 7.00-8.20 (m, 9H); ^{13}C nmr 34.4 (C-5), 42.1 and 42.5 (C-3 and C-6), 54.1 (C-2), 58.9 (CH_2OH), 64.2 (NCHPh), 115.2, 120.9, 123.8, 124.7, 126.3, 126.7, 128.0, 129.1, 129.3, 133.9, 206.7 (CO); ms (m/z, %) 475 (1), 443 (70), 412 (100), 367 (99), 271 (54), 196 (12), 143 (51), 106 (60).

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