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Synthetic Applications of 2-(1,3-Dithian-2-yl)indoles V.[1] Asymmetric Synthesis of Dasycarpidone-Type Indole Alkaloids

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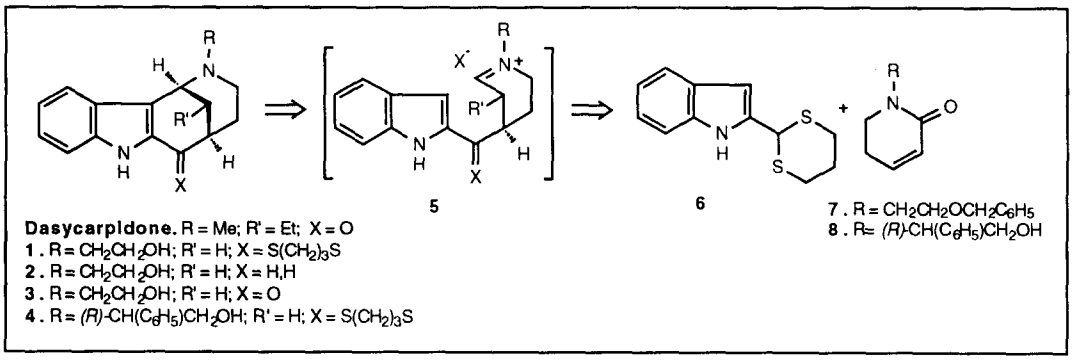
Abstract– Chiral tetracyclic dasycarpidone-type compounds *(αR, 1S, 5R)*-**4** and *(αR, 1R, 5S)*-**16** have been synthesized from 2-(1,3-dithian-2-yl)indole **6** and (α*R*)-*N*-(β-hydroxy-α-phenylethyl)-Δ^3-piperidein-2-one **8** in three steps, following the methodology that we described recently.

Continuing our studies on the synthesis of indole alkaloids by the use of 2-(1,3-dithian-2-yl)indoles (**6**) as umpoled synthons, we described recently the synthesis of dasycarpidone type compound **1** (Scheme 1).[1,2] Thus, the conjugate addition of **11**, the dianion of **6**, on Δ^3-piperidein-2-one **7**, followed by reductive cyanation of the resulting adduct and aqueous AcOH cyclization was shown to be a straightforward method for the preparation of the tetracyclic ABED systems, key intermediates in the synthesis of *Strychnos* alkaloids.[3-6] We describe now the application of the methodology to the preparation of chiral dasycarpidone system **4** and its diastereomer **16** by the use of Δ^3-piperidein-2-one **8**, an asymmetric equivalent of **7**.



5 6

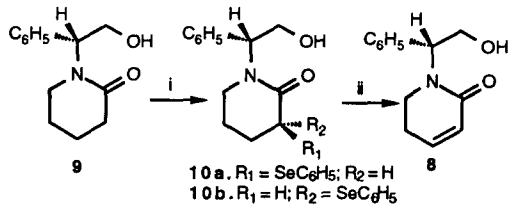
Dasycarpidone. R = Me; R' = Et; X = O
1. R = CH_2CH_2OH; R' = H; X = $S(CH_2)_3S$
2. R = CH_2CH_2OH; R' = H; X = H,H
3. R = CH_2CH_2OH; R' = H; X = O
4. R = *(R)*-$CH(C_6H_5)CH_2OH$; R' = H; X = $S(CH_2)_3S$

7. R = $CH_2CH_2OCH_2C_6H_5$
8. R = *(R)*-$CH(C_6H_5)CH_2OH$

Scheme 1

The synthesis of compound **8** has been developed in the context of studies on the reactivity of its precursor, lactam **9**.[7] Phenylselenylation of lactam **9** followed by MCPBA oxidation of the selenyl derivative **10**, using slight

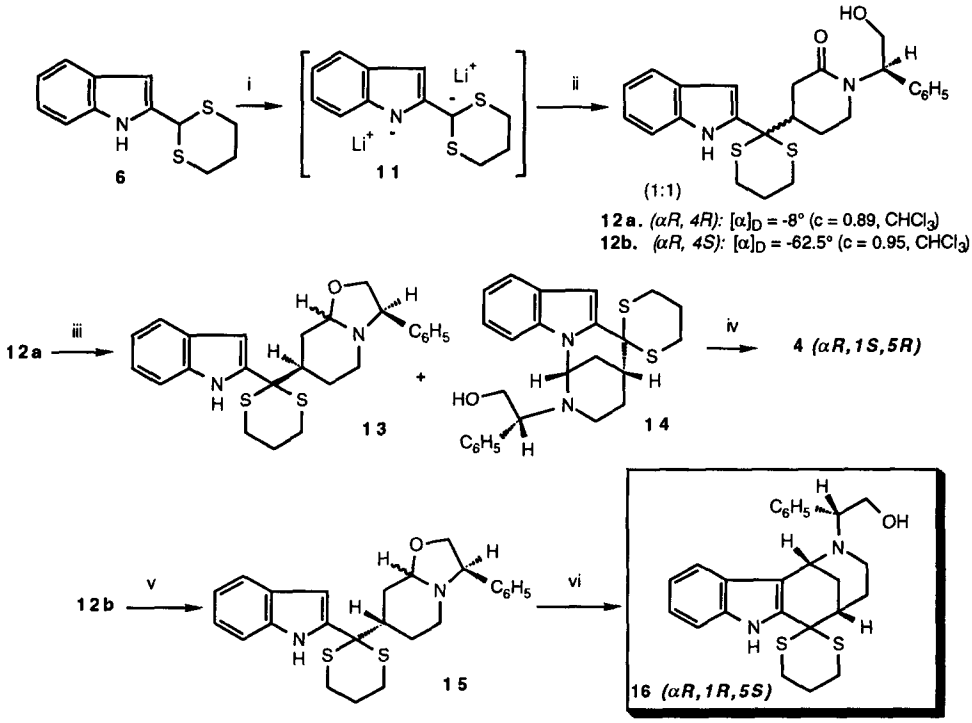
modifications of the method applied for the preparation of **7**,[1] yielded **8** (Scheme 2), which was identified from its spectral data.[8]



Reagents and conditions: i) 1. *sec*-BuLi (2.5 equivalents), THF, -78°C, 20 min; 2. C_6H_5SeBr (1.1 equivalents), -78°C, 1 h (64%, **10a:10b** = 7:3); ii) MCPBA (1.1 equivalents), CH_2Cl_2, 0°C to room temperature, 30 min (95%).

Scheme 2

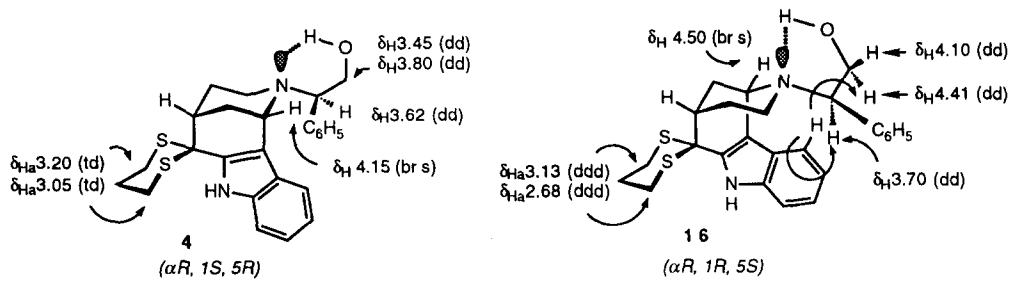
Condensation of 2 equivalents of dithianylindole dianion **11** with 1 equivalent of piperideinone **8** in THF at -78°C yielded an equimolecular mixture of diastereomeric lactams **12a** and **12b**, epimers on C-4 (88%) which were easily separated by flash column chromatography (Scheme 3). As expected, both diastereomers showed very similar NMR data. The main spectral differences observed between lactams **12** were the ^{13}C NMR signals corresponding to C-6 and C-α, which were 1.3 ppm shielded in **12b**.[9] The partial reduction of the carbonyl group was carried out with an excess of Red-Al® in THF.[10]



Reagents and conditions: i) *n*-BuLi (2.1 equivalents), THF, -78°C; ii) **8** (0.5 equivalents), -78°C, 5 h (88% based on **8**); iii) RedAl® (excess), THF, -78°C to r.t., 8 h (45% on transformed product); iv) 50% aq. AcOH, CH_2Cl_2, r.t., 8 h (55%); v) Red-Al® (excess), THF, -45°C, 30 min, 2 h (56%); vi) 50% aq. AcOH, CH_2Cl_2, 2 h (84%).

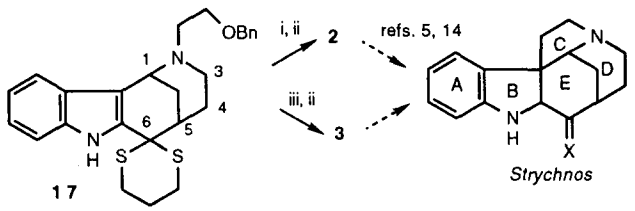
Scheme 3

In the case of **12a** the formation of aminal **14** was observed together with the expected oxazolidines **13**, obtained as a mixture of epimers on C-2. The reduction of compound **12b** occurred much faster to give exclusively the corresponding oxazolidines **15**. The most characteristic NMR data for all oxazolidines were the signals correponding to 2-position: δ_H~3.7, δ_C~90. Tetracyclic compound **4**[11] was obtained by treating the mixture of oxazolidines **13** and aminal **14** with 50% aqueous AcOH at room temperature.[12] Compound **16**[13] was similarly prepared from oxazolidines **15**, and once again the reaction proved to be much easier when the starting compounds were *(αR, 4S)*. Such different behavior, and the splitting of the aromatic signals in the ^{1}H NMR spectrum of **4**, can be attributed to the steric hindrance between the α-phenyl ring and the piperidine C-2 substituent in the *(αR, 4R)* series.



Scheme 4. Double arrows indicate NOESY correlations.

In addition, the transformation of racemic tetracyclic compound **17**[1] to compounds **2** and **3**[8] has been carried out by Raney-Nickel reduction of the dithiane ring and by $(CF_3COO)_2IPh$ deprotection of the C-6 carbonyl group respectively, followed by *O*-debenzylation. Since the closure of ring C from compounds type **2** has already been described,[14] its preparation constitutes a new formal synthesis of the *Strychnos* pentacyclic framework. By extrapolation to the chiral series this work opens a new perspective on the preparation of *Strychnos* alkaloids.



Reagents and conditions: i) W-2 Raney-Ni (excess), EtOH, reflux, 4 h (70%); ii) Me_2S (excess), $BF_3.Et_2O$ (10.6 equivalents), CH_2Cl_2 (~90%); iii) $(CF_3COO)_2IC_6H_5$ (1.4 equivalents), CH_3CN, r.t., 45 min (83%).

Scheme 5

By applying our methodology, we have achieved the synthesis of chiral dasycarpidone type tetracyclic systems **4** and **16** in three steps from indolyldithiane **6** and asymmetric Δ^3-piperidein-2-one **8** . Further work will aim at the chiral synthesis of *Strychnos* pentacyclic framework.

Acknowledgements

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References and notes

1. For part IV see: Diez, A.; Castells, J.; Forns, P.; Rubiralta, M.; Grierson, D.S.; Husson, H.-P.; Solans, X.; Font-Bardia, M. *Tetrahedron*, **1994**, *50*, 6585-6602.
2. Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.*, **1994**, *59*, 3939-3951, and references cited therein.
3. For a review see: Bosch, J.; Bonjoch, J. "Pentacyclic *Strychnos* Alkaloids". In *Studies in Natural Products Chemistry*; Atta-ur-Rahman; Ed. Elsevier: Amsterdam, **1988**, Vol. I, pp. 31-88.
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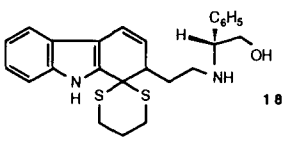
5. Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.*, **1990**, *55*, 6299-6312.
6. Gràcia, J.; Bonjoch, J.; Casamitjana, N.; Amat, M.; Bosch, J. *J. Chem. Soc., Chem. Commun.*, **1991**, 614-615.
7. Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.*, **1994**, *35*, 2529-2532.
8. All compounds have been fully characterized by their spectral data and elemental analysis or HRMS.
9. The absolute configuration of C-4 in compounds **12a** and **12b** was determined on the basis of the stereochemistry of the corresponding cyclization products **16** and **4**.
10. Reaction with Red-Al® avoided the further reduction to the corresponding piperidine, observed when using $LiAlH_4$.
11. Compound **4**: $[\alpha]_D$ = -17° (c = 1.1, EtOH); ^1H NMR (300 MHz, $CDCl_3$) 1.90-2.45 (m, 7H), 2.70-2.95 (m, 4H), 3.05 and 3.20 (2 td, *J* = 12 and 2 Hz, 2H, SCH_a), 3.45 (dd, *J* = 9 and 2 Hz, 1H, CH_AOH), 3.62 (dd, *J* = 4 and 2 Hz, 1H, CHα), 3.80 (dd, *J* = 9 and 4Hz, 1H, CH_BOH), 4.15 (br s, 1H, 1-H), 7.05 (t, *J* = 7 Hz, 1H, 10-H), 7.15 (t, *J* = 7 Hz, 1H, 9-H), 7.27-7.55 (m, 3H, Ph-*p* , 8-H and 11-H), 7.49 (t, *J* = 7 Hz, 2H, Ph-*m*), 7,64 (d, *J* = 7 Hz, 2H, Ph-*o*), 8.60 (br s, 1H, NH).
12. Treatment of oxazolidines **13** in refluxing aqueous AcOH yielded compounds **18**, as the result of a fragmentation of intermediate **4**. **18** (Diastereomeric mixture): ^1H NMR (300 MHz, $CDCl_3$) 2.10 (br t, *J* = 7 Hz, 2H, CH_2), 2.80-2.95 (m, 7H, SCH_2CH_2, and CH), 3.25 (t, *J* = 7 Hz, 2H, NCH_2), 3.50 (dd, *J* = 9 and 7 Hz, 1H, CH_AOH), 3.69 (dd, *J* = 9 and 4 Hz, 1H, CH_BOH), 3.72 (dd, *J* = 7 and 4 Hz, 1H, CHα), 7.11 (d, *J* = 7 Hz, 1H, CH=), 7.15-7.60 (m, 8H, Ar-H), 7.95 (d, *J* = 7 Hz, 1H, CH=), 8.03 (d, *J* = 7 Hz, 1H, 5-H), 8.60 (br s, 1H, In-NH).



18

13. Compound **16**: $[\alpha]_D$ = -37.5° (c = 1.23, EtOH); ^1H NMR (500 MHz, $CDCl_3$) 1.87-1.92 (m, 1H, 4-H_a), 1.95 (qt, *J* = 14 and 2 Hz, 1H, SCH_2CH_a), 2.04 (td, *J* = 12 and 2.5 Hz, 1H, 3-H_a), 2.11 (dm, *J* = 14 Hz, 1H, SCH_2CH_e), 2.14 (dm, *J* = 12 Hz, 1H, 12-He), 2.22 (dm, *J* = 11 Hz, 1H, 4-He), 2.44 (ddd, *J* = 12, 6 and 3 Hz, 1H, 12-H_a), 2.68 (dt, *J* = 14 and 2 Hz, 1H, SCH_e), 2.71 (dt, *J* = 14 and 2 Hz, SCH_e'), 2.72-2.76 (m, 1H, 5-He), 2.92 (ddd, *J* = 14, 12 and 2 Hz, 1H, SCH_a), 3.13 (td, *J* = 14, 12 and 2 Hz, 1H, SCH_a'), 3.70 (dd, *J* = 4 and 2 Hz, 1H, CHα), 4.10 (dd, *J* = 10 and 2 Hz, 1H, CH_AOH), 4.41 (dd, *J* = 10 and 4 Hz, 1H, CH_BOH), 4.50 (br s, 1H, 1-H), 7.12 (t, *J* = 7 Hz, 1H, 10-H), 7.14-7.22 (m, 6H, Ph-H and 9-H), 7.36 (d, *J* = 7 Hz, 1H, 8-H), 7.59 (d, *J* = 7 Hz, 1H, 11-H), 8.73 (br s, 1H, NH); ^{13}C NMR 24.5 (SCH_2CH_2), 26.6 (C-4), 28.9 and 29.1 (SCH_2), 31.4 (C-12), 33.3 (C-5), 42.1 (C-3), 51.9 (C-1), 53.4 (SCS), 63.4 (C-β), 66.5 (C-α), 111.3 (C-8), 119.2 (C-11), 120.4 (C-10), 122.6 (C-9), 128.3 (Ph-*o* and Ph-*m*), 128.7 (Ph-*p*).
14. For the cyclization of the 4-ethyl derivative, see: Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.*, **1990**, *31*, 5089-5092.

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