Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 95–106

TETRAHEDRON: *ASYMMETRY*

Addition of chiral enolates to *N*-alkyl-3-acylpyridinium salts. Total synthesis of (+)-16-epivinoxine and (−)-vinoxine

M.-Lluïsa Bennasar,[a,*] Ester Zulaica,[a] Yolanda Alonso,[a] Bernat Vidal,[a] Jesús T. Vázquez[b] and Joan Bosch[a]

[a]*Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain*
[b]*Instituto Universitario de Bio-Orgánica 'Antonio González', University of La Laguna, 38206-La Laguna, Tenerife, Spain*

Received 29 January 2002; accepted 4 February 2002

Abstract—Chiral enolates of indolylacetyl derivatives **6a–f** undergo addition to pyridinium salt **7** with complete *trans*-selectivity and varied diastereofacial selectivities to give, after acid-induced cyclization of the intermediate 1,4-dihydropyridines, the vinoxine-related tetracycles **8a–f**. Starting from (*S*)-prolinol indolylacetamide **6e**, subsequent elaboration of the ethylidene substituent from tetracycle **8e** and removal of the chiral auxiliary has resulted in a straightforward synthesis of (+)-16-epivinoxine and (−)-vinoxine.

1. Introduction

The nucleophilic addition of indole-containing enolates to *N*-alkyl-3-acylpyridinium salts has been extensively used in our laboratory as the initial step of a general scheme for the synthesis of indole alkaloids.[1,2] After suitable manipulation of the resultant indolyl-1,4-dihydropyridine adducts, it is possible to construct complex polycyclic structures, giving access to alkaloids belonging to different structural types. Thus, starting from the enolates derived from 1-, 2-, and 3-indoleacetates, we have synthesized indole alkaloids of the C-mavacurine[3] and *Strychnos* groups,[4] as well as tetracyclic akuammiline substructures.[5] From 2-acetylindole enolates, we have completed total syntheses of bridged (ervitsine) and fused 2-acylindole alkaloids of the ervatamine and silicine groups.[6] In a similar manner, we have developed formal syntheses of the Corynanthean alkaloids geissoschizine and akagerine starting from 1-acetylindole enolates.[7] So far, all these syntheses have only been carried out in the racemic series.

We have consequently become interested in exploring the stereoselective version of the above methodology, using either chiral non-racemic enolates or chiral non-racemic pyridinium salts. In this manner, the scope and potential of 1,4-dihydropyridines as effective building blocks for alkaloid synthesis would be significantly enhanced. In the literature there are several examples of stereoselective syntheses of chiral non-racemic 1,4-dihydropyridines[8] by diastereofacial-selective addition of organometallic reagents to *N*-acylpyridinium salts bearing chiral auxiliaries at the 3-position of the ring.[9] However, the application of similar auxiliary-induced stereoselective processes in the alkaloid field is far less common.[9e,10] In this context, we have recently described a biomimetic synthesis of (−)-$N_{(a)}$-methylervitsine, starting from a chiral *N*-alkylpyridinium salt.[11] On the other hand, Spitzner has used the addition of a chiral non-racemic nucleophile to a pyridinium salt in the synthesis of (−)-isovallesiachotamine and (+)-vallesiachotamine.[12] We wish to report herein our work on the stereoselective synthesis of vinoxine, which has provided access to (+)-16-epivinoxine and the natural product, (−)-vinoxine.

Vinoxine **1** is a C-mavacurine alkaloid isolated in 1967 from *Vinca minor* L,[13] with a tetracyclic bridged structure[14] lacking the tryptamine unit present in the majority of indole alkaloids. The (3*S*)-absolute configuration of natural (−)-vinoxine was established by comparing its CD curves with those of its pentacyclic analogue pleiocarpamine.[14b] The 15-H/16-H relative configuration, initially reported to be *trans*, was reassigned several years later as *cis* (Fig. 1).[3a,15]

Scheme 1 outlines our previously described synthesis of (±)-vinoxine.[3a] The tetracyclic ring system of the alka-

* Corresponding author. Tel.: 34-934024540; fax: 34-934024539; e-mail: bennasar@farmacia.far.ub.es

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00055-1

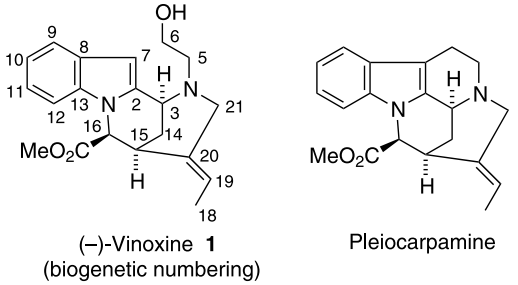
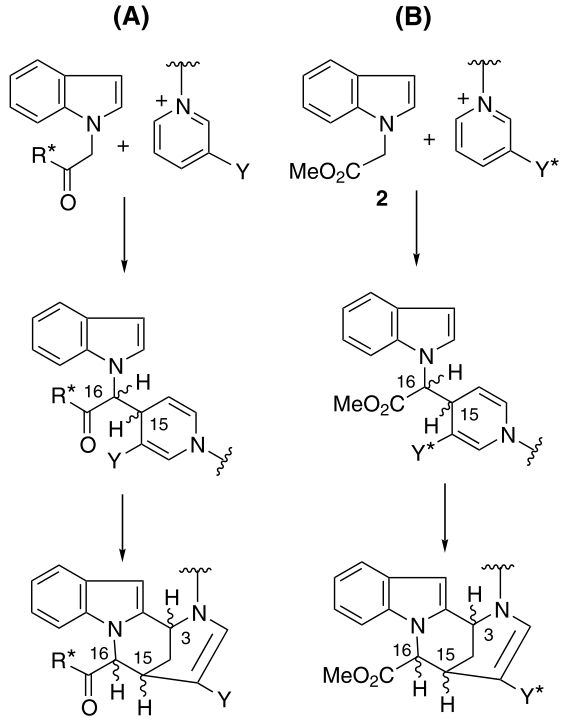


Figure 1.

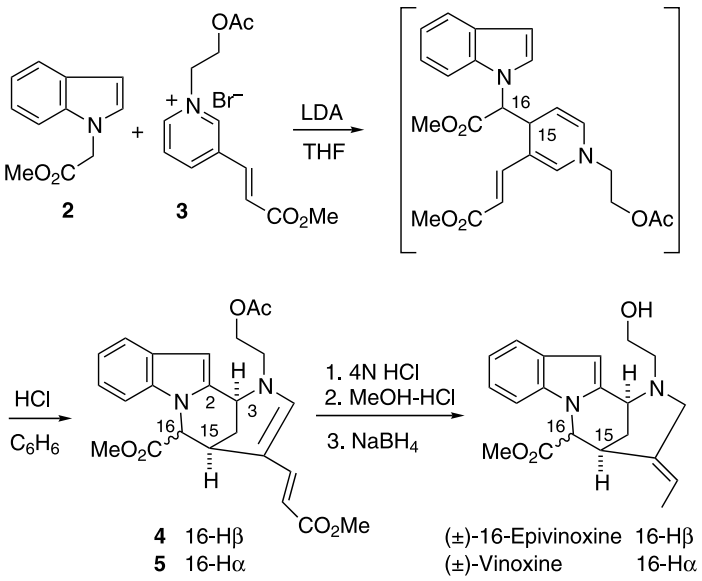
loid was assembled in a straightforward manner, by a one-pot process involving the addition of the enolate derived from methyl 1-indoleacetate **2** to pyridinium salt **3** (formation of C(15)–C(16) bond), followed by the in situ acid-induced cyclization of the initially formed 1,4-dihydropyridine (formation of C(2)–C(3) bond). As a result, a 5:1 C(16) epimeric mixture of tetracycles **4** (15-H/16-H *trans* relative configuration) and **5** (15-H/16-H *cis* relative configuration) was obtained in 40% yield. Subsequent stereoselective elaboration of the (*E*)-ethylidene substituent was effected following a classical procedure in indole alkaloid synthesis,[16] by hydrolysis-decarboxylation of the 3-(tetrahydro-3-pyridyl)acrylate moiety, reesterification of the C-16 methoxycarbonyl group, and final reduction with $NaBH_4$. In this manner, (±)-vinoxine and minor amounts of its C(16) epimer, (±)-16-epivinoxine, were obtained in 30% yield.

2. Results and discussion

Two strategies can be envisaged for the stereoselective version of the above racemic synthesis: incorporating a chiral group either at the indolylacetyl moiety of the nucleophile (A) or at the 3-position of the pyridine ring (B) (Scheme 2). In both cases, this group would act as a chiral auxiliary, thus allowing the stereoselective generation of the stereocenter at the pyridine 4-position C(15). Cyclization of the resultant 1,4-dihydropyridine onto the indole nucleus would result in the generation of the C(3) stereocenter, whose configuration would be determined by that of C(15) because of the bridgehead character of both carbons. The important role played by the electron-withdrawing group Y ($CH{=}CHCO_2Me$) at the 3-position of the pyridine ring in the previous racemic synthesis prompted us to study the feasibility of strategy A, which enabled us to maintain the same group.



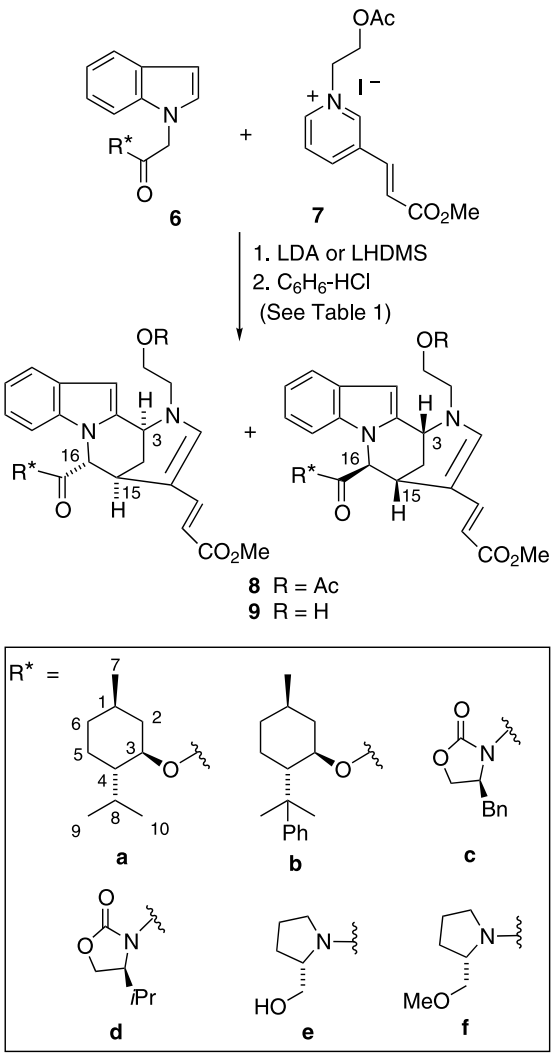
Scheme 2. Strategies for the stereoselective synthesis of vinoxine.



Scheme 1. Synthesis of (±)-vinoxine and (±)-16-epivinoxine.

As chiral analogues of methyl 1-indoleacetate **2**, we selected the indolylacetyl derivatives **6** (Scheme 3), which contain chiral auxiliaries[17] commonly used in diastereoselective Michael additions to prochiral enones and α,β-unsaturated esters.[18] Thus, (1*R*)-menthyl and (1*R*)-8-phenylmenthyl esters **6a** and **6b**, *N*-acyloxazolidinones **6c** and **6d**, and (*S*)-prolinol indolylacetamides **6e** and **6f** were prepared according to standard procedures[19] (see Section 4), and the behavior of their corresponding enolates in the nucleophilic addition–dihydropyridine cyclization sequence with pyridinium iodide **7** was investigated.

The results, summarized in Table 1, present some general trends. The best yields (37–49%) of the vinoxine related tetracycles **8** and **9**, the latter resulting from hydrolysis of the acetate moiety, were obtained when ester enolates were used as nucleophiles (entries 1–3). The use of imide (entries 4 and 5) and amide (entries 6 and 7) enolates was less efficient. Although in all cases the addition–cyclization process took place with complete diastereoselectivity since only tetracycles with 15-H/16-H *trans* relative configuration were detected,[20] the above chiral enolates derived from **6** showed moderate



Scheme 3.

Table 1. Addition–cyclization sequence from chiral enolates derived from **6** and pyridinium iodide **7**

Entry	Indole[a]	Product (%)[b]	Diastereomeric ratio[c]
1	**6a**	**8a** (40)	1:1[d]
2	**6b**	**8b** (28)	2.5:1[d]
		9b (9)	1:1[d]
3	**6b**	**8b** (28)	2:1[d]
		9b (21)	1:1[d]
4	**6c**	**8c** (30)	1.5:1
5	**6d**	**8d** (31)	1.4:1
6	**6e**	**8e** (25)	3:1
7	**6f**	**8f** (10)	1:1[d]

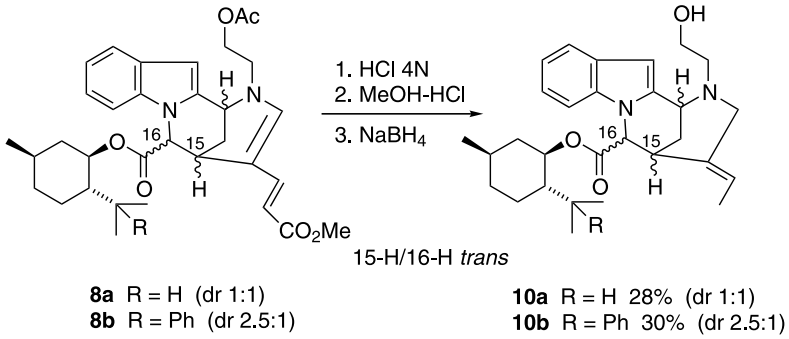
[a] Generation of the enolate with LDA (LHDMS in entries 1 and 2).
[b] Isolated yields.
[c] Approximate ratio calculated by ^{1}H NMR.
[d] Unseparable diastereomeric mixture.

to low facial diastereoselectivity in their reactions with pyridinium salt **7**.

Previous studies on the use of cyclohexyl-based chiral auxiliaries in different reaction types indicate that (1*R*)-8-phenylmenthol[21] induces high levels of stereocontrol in comparison with (1*R*)-menthol, which generally gives poorer results.[22,23] In our case, no diastereoselectivity was observed when the enolate derived from (1*R*)-menthyl ester **6a**, generated with LHDMS, was treated with pyridinium salt **7** (entry 1), but only slightly better results were obtained from (1*R*)-8-phenylmenthyl ester **6b** under the same conditions (entry 2). The use of LDA as the base to generate the enolate of **6b** did not improve the diastereoselectivity, although the overall yield of tetracycles **8b** and **9b** increased (entry 3).

The synthetic utility of the above reactions was hampered by the difficulty in separating the diastereomeric mixtures of tetracycles **8a**, **8b** or **9b** by column chromatography. Furthermore, the chiral auxiliary of **8a** or **8b** could not be removed under the usual (basic hydrolysis or methanolysis) conditions or under the acidic hydrolytic conditions required for the formation of the (*E*)-ethylidene substituent from the 3-(tetrahydro-3-pyridyl)acrylate moiety. Thus, treatment of diastereomeric mixtures of **8a** or **8b** with 4N aqueous HCl at reflux, followed by $NaBH_4$ reduction gave the auxiliary-containing (*E*)-ethylidene derivatives **10a** or **10b** in 28 and 30% yields, respectively (Scheme 4).

On the other hand, the use of *N*-acyloxazolidinones **6c** and **6d** in the addition–cyclization sequence was unsatisfactory as poor diastereomeric ratios of the respective tetracycles **8c** and **8d** were obtained in 30% yields (entries 4 and 5). This result was completely unexpected since it is well known that substituted 2-oxazolidinones are excellent chiral auxiliaries,[24,25] which have been used successfully in a variety of diastereoselective transformations.[26] The diastereomeric mixtures of **8c** or **8d** were easily separated by column chromatography, although the absolute configuration of the diastereomers was not determined. Both diastereomers of **8c** were independently treated with LiOOH in order



Scheme 4.

to remove the chiral auxiliary.[27,28] However, although (*S*)-4-benzyl-2-oxazolidinone was recovered in both cases in ~60% yield, only minor amounts (5%) of the desired tetracycles (+)-**11** (from the minor diastereomer **8c**) or (−)-11 (from the major diastereomer **8c**) were obtained after esterification of the crude reaction products (Scheme 5).

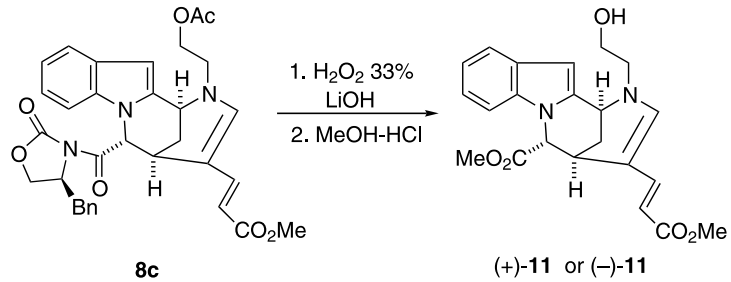
Although less popular than *N*-acyloxazolidinones, *N*-acyl derivatives of (*S*)-prolinol and their ethers have also been used as substrates for diastereoselective reactions,[24,25] in particular, alkylations.[29,30] In our case, indolylacetamides **6e** and **6f** behaved quite differently in their reactions with pyridinium salt **7**. Thus, whereas **6f** led to a nearly equimolecular mixture of diastereomers **8f** in low yield (10%, entry 7), the addition of the dianion of **6e** to pyridinium salt **7**, followed by in situ acid-induced cyclization afforded a 3:1 diastereomeric mixture of tetracycles **8e** (25% yield, entry 6), which were easily separated by column chromatography. The minor diastereomer, a very polar compound, was not isolated in all runs. The absolute configuration of the major diastereomer (+)-**8e** was assigned as 3*S*,15*S* since it was ultimately converted to (+)-16-epivinoxine and (−)-vinoxine (see below).

The stereochemical course of the above reaction can be rationalized as follows. The 15-H/16-H *trans* configuration of both diastereomeric tetracycles **8e** (and all tetracycles **8**) is a consequence of the preferred *ul* approaches between the dianion derived from **6e** and pyridinium salt **7**, as depicted in Scheme 6. On the other hand, the absolute configuration 3*S*,15*S* of the major diastereomer (+)-**8e** implies that the *Z*-configurated, conformationally locked dianion **6e**·2Li preferentially reacts with **7** from its *Re* face (i.e. the opposite face to that of the 2-hydroxymethyl substituent), as generally occurs in the reactions of (*S*)-prolinol amide enolates.[24]

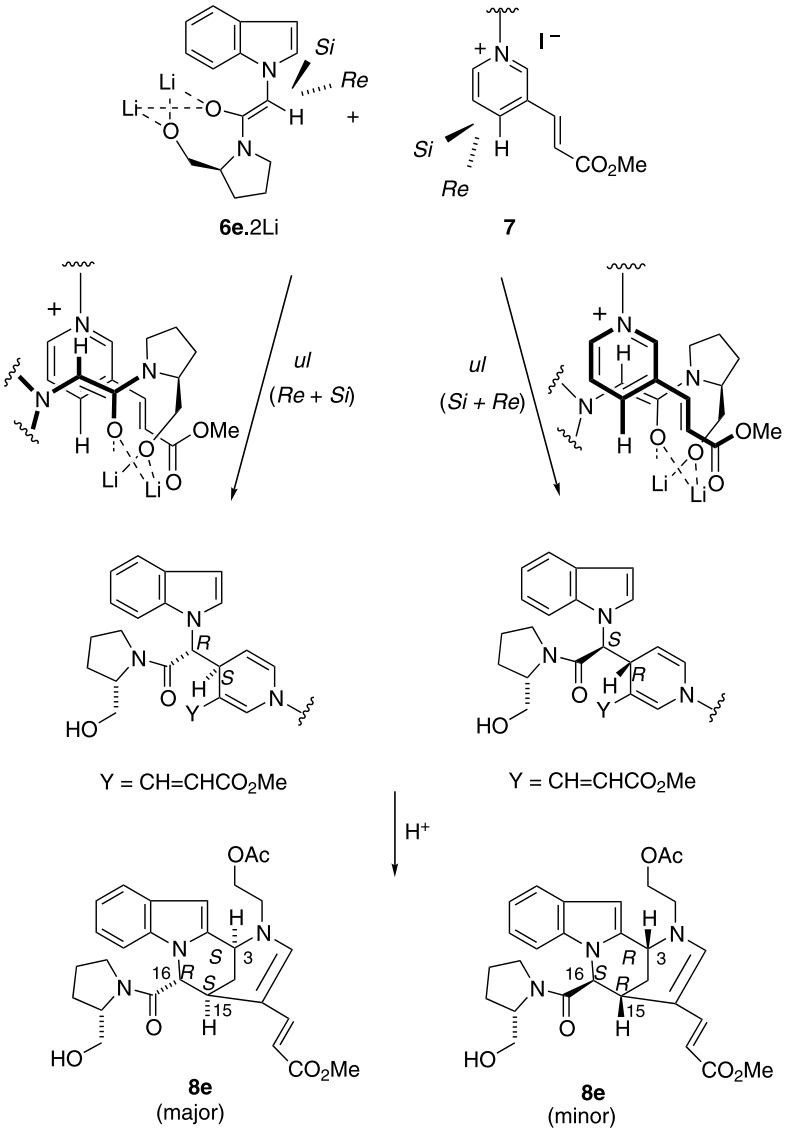
With the major diastereomer (+)-**8e** in hand, access to the alkaloid vinoxine only required the removal of the chiral auxiliary and the elaboration of the (*E*)-ethylidene substituent by means of the usual hydrolysis–decarboxylation procedure. Knowing that (*S*)-prolinol amides are efficiently hydrolyzed under acidic conditions,[24] we initially considered carrying out both transformations in a single synthetic step. However, treatment of (+)-**8e** with 4N HCl at reflux followed by $NaBH_4$ reduction gave the (*E*)-ethylidene derivative **12** (33%), which contains a 2-pyrrolidinylmethyl ester coming from an intramolecular *O*-acylation.[24] Complete removal of the auxiliary was accomplished by transesterification of **12** with MeOMgBr to give (+)-16-epivinoxine **13** in 50% yield (Scheme 7). Then, (+)-16-epivinoxine **13** could be partially epimerized to a 2:1 mixture (calculated by ^{1}H NMR) of **13** and (−)-vinoxine **1** by treatment with *t*-BuOK in MeOH at reflux. These synthetic vinoxines showed NMR spectra identical to those of the racemic materials.[3a]

After flash chromatography, the above ratio of **13**/**1** was shifted to 14:86 (calculated by HPLC). Considering the specific rotation of the isolated components, (+)-**13**, $[\alpha]_D$ +109 (*c* 0.11, $CHCl_3$), and (−)-**1**, $[\alpha]_D$ −18.6 (*c* not given, $CHCl_3$),[14b] the specific rotation $[\alpha]_D$ +4 (*c* 0.1, $CHCl_3$) of this mixture agrees with the levorotatory character of **1**.

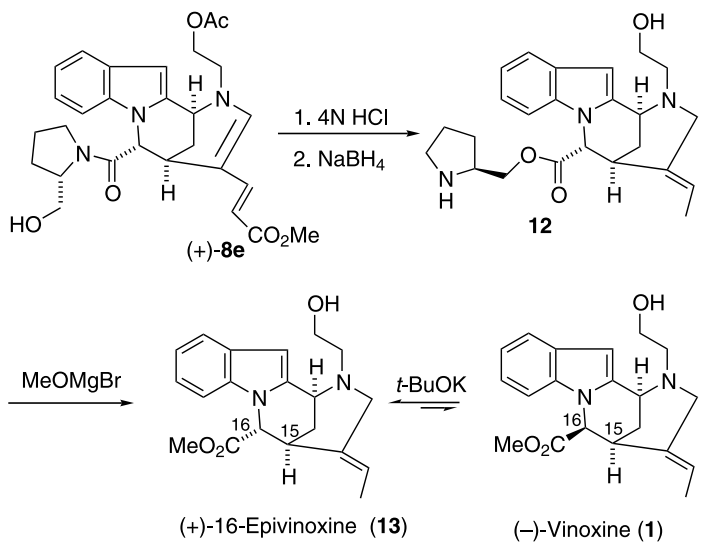
Finally, the (3*S*)-absolute configuration of both vinoxines was unambiguously established by comparing their CD data with those reported for natural (−)-**1**.[14b] Thus,



Scheme 5.



Scheme 6.



Scheme 7. Synthesis of (+)-16-epivinoxine and (−)-vinoxine.

the CD curves displayed an analogous course, exhibiting Cotton effects of the same sign at the typical λ_{max} of the indole chromophore: a negative Cotton effect at ~225 nm and two broad positive Cotton effects at ~270 and ~295 nm.

3. Conclusion

In conclusion, the role of a series of chiral analogues of methyl 1-indoleacetate in the nucleophilic addition–dihydropyridine cyclization sequence with pyridinium salt **7** has been investigated. When the enolate derived from (*S*)-prolinol indolylacetamide **6e** is used as the nucleophile, this sequence provides stereoselective access to (+)-16-epivinoxine and natural (−)-vinoxine.

4. Experimental

4.1. General

All non-aqueous reactions were performed under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (pre-coated F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotary evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Melting points are uncorrected. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75.4 MHz, respectively, using TMS as an internal reference. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

4.2. (1*R*,3*R*,4*S*)-Menthyl 1-indoleacetate 6a

A mixture of 1-indoleacetic acid (0.93 g, 5.3 mmol), DMAP (0.56 g, 4.25 mmol), DCC (0.72 g, 5.8 mmol), and (−)-menthol (0.89 g, 5.3 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 6 days and then filtered. The filtrate was concentrated and the residue was chromatographed (hexanes and 95:5 hexanes–AcOEt, increasing polarity) to afford ester **6a** (0.95 g, 57%); $[\alpha]_D^{22}$ −43.5 (*c* 1, $CHCl_3$); IR (film) 1749, 1733; ^1H NMR (assignment aided by HMQC) δ 0.63, 0.78, 0.88 (3d, $J=6.6$ Hz, 9H, 7′-, 9′-, and 10′-H), 0.90 (m, 3H), 1.23 (tm, $J=12$, 12 Hz, 1H, 4′-H), 1.42 (m, 1H, 1′-H), 1.60 (m, 3H), 1.95 (dm, $J=12$ Hz, 1H, 2′-H), 4.65 (td, $J=12$, 12, 3.7 Hz, 1H, 3′-H), 4.81 (s, 2H, NCH_2), 6.55 (d, $J=3$ Hz, 1H, 3-H), 7.08–7.23 (m, 4H, indole), 7.60 (d, $J=8$ Hz, 1H, 4-H); ^{13}C NMR (assignment aided by HMQC δ 16.1 (C-7′), 20.6, 21.9 (C-9′, C-10′), 23.2 (C-6′), 26.0 (C-8′), 31.3 (C-1′), 34.0 (C-5′), 40.6 (C-2′), 46.7 (C-4′), 48.1 (NCH_2), 75.8 (C-3′), 102.2 (C-3), 108.8 (C-7), 119.6 (C-4), 120.9 (C-5), 121.8 (C-6), 128.4 (C-2), 128.5 (C-3a), 136.4 (C-7a), 168.0 (CO). Anal. calcd for $C_{20}H_{27}NO_2 \cdot 1/2H_2O$: C, 74.49; H, 8.74; N, 4.34. Found: C, 74.40; H, 8.61; N, 4.32%.

4.3. (1*R*,3*R*,4*S*)-8-Phenylmenthyl 1-indoleacetate 6b

A solution of indole (0.5 g, 4.27 mmol) in DMF (7.5 mL) was added to a suspension of NaH (60%, 0.25 g, 10.6 mmol) in DMF (3 mL) and the resulting mixture was stirred at rt for 1 h. Then (+)-(1*R*,3*R*,4*S*)-8-phenylmenthyl 2-chloroacetate (1.32 g, 4.27 mmol) was added at 0°C and the mixture was stirred at rt for 3 h. The reaction mixture was poured into ice-H_2O and extracted with Et_2O. Concentration of the ethereal extracts followed by flash chromatography (8:2 hexanes–Et_2O) afforded ester **6b** (1.3 g, 78%); $[\alpha]_D^{22}$ +32.5 (*c* 1.2, CCl_4); IR (film) 1748; ^1H NMR (assignment aided by HMQC) δ 0.86 (d, $J=6.5$ Hz, 3H, CH_3), 0.94 (m, 2H, 2′- and 6′-H), 1.14 (m, 2H, 5′-H), 1.18, 1.28 (2s, 6H, CH_3), 1.69 (m, 1H, 1′-H), 1.77 (m, 1H, 2′-H), 1.82 (m, 1H, 6′-H), 2.09 (m, 1H, 4′-H), 3.87, 4.15 (2d, $J=15$ Hz, 2H, NCH_2), 4.87 (td, $J=11$ and 4.4 Hz, 1H, 3′-H), 6.48 (d, $J=3$ Hz, 1H, 3-H), 6.90 (d, $J=3$ Hz, 1H, 2-H), 7.06–7.37 (m, 3H, indole), 7.59 (d, $J=8$ Hz, 1H, 4-H); ^{13}C NMR (assignment aided by HMQC δ 21.6 (C-7′), 22.8, 29.6 (C-9′, C-10′), 26.8 (C-5′), 31.0 (C-1′), 34.2 (C-6′), 39.3 (C-8′), 41.4 (C-2′), 47.2 (NCH_2), 49.8 (C-4′), 75.3 (C-3′), 101.9 (C-3), 108.8 (C-7), 119.5 (C-4), 120.8 (C-5), 121.6 (C-6), 125.1 (C-2), 125.3, 127.9, 128.3 (C-3a, Ph), 136.2 (C-7a), 151.8 (Ph), 167.8 (CO). Anal. calcd for $C_{26}H_{31}NO_2 \cdot 1/2H_2O$: C, 78.36; H, 8.09; N, 3.51. Found: C, 78.40; H, 7.97; N, 3.57%.

4.4. (*S*)-*N*-(1-Indolyl)acetyl-4-benzyl-2-oxazolidinone 6c

Pivaloyl chloride (1.42 mL, 10.5 mmol) was slowly added to a solution of 1-indoleacetic acid (1.84 g, 10.5 mmol) and TEA (1.6 mL, 11.5 mmol) in THF (26 mL) cooled at 0°C, and the resulting whitish suspension was stirred at 0°C for 1 h. In a second flask, *n*-BuLi (10.5 mmol) was added to a solution of (*S*)-4-benzyl-2-oxazolidinone (2.16 g, 10.5 mmol) in THF (105 mL) cooled at −78°C. The mixture was stirred at −78°C for 30 min, and then added to the above suspension cooled at −78°C. The reaction mixture was allowed to warm to rt (2 h), poured into a saturated aqueous NH_4Cl solution, and extracted with Et_2O. The organic extracts were washed with a saturated aqueous $NaHCO_3$ solution, dried and concentrated. The resulting residue was chromatographed (flash, 1:1 hexanes–AcOEt) to afford compound **6c** (2.24 g, 64%); mp 131°C (hexanes–Et_2O–acetone); $[\alpha]_D^{22}$ +69.7 (*c* 0.3, MeOH); IR (KBr) 1781, 1712; ^1H NMR δ 2.81 (dd, $J=13.3$, 8.8 Hz, 1H), 3.29 (dd, $J=13.3$, 3.3 Hz, 1H), 4.30 (m, 2H), 4.67 (m, 1H), 5.46, 5.54 (2d, $J=18.4$ Hz, 2H), 6.61 (d, $J=0.3$ Hz, 1H), 7.12–7.32 (m, 8H), 7.66 (d, $J=8$ Hz, 1H); ^{13}C NMR δ 37.5 (CH_2), 49.4 (CH_2), 55.1 (CH), 67.1 (CH_2), 102.6 (CH), 108.8 (CH), 119.8 (CH), 121.1 (CH), 121.9 (CH), 127.4 (CH), 128.2 (C), 128.9, 129.3, 128.6 (CH), 134.4 (C), 136.6 (C), 153.6 (C), 168.0 (C). Anal. calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.42; N, 8.38. Found: C, 71.92, H, 5.43, N, 8.30%.

4.5. (*S*)-*N*-(1-Indolyl)acetyl-4-isopropyl-2-oxazolidinone 6d

As in the preparation of oxazolidinone **6c**, from 1-indoleacetic acid (0.2 g, 1.14 mmol), triethylamine (0.17

mL, 1.25 mmol), pivaloyl chloride (0.15 mL, 1.25 mmol), (*S*)-4-isopropyl-2-oxazolidinone (0.16 g, 1.26 mmol) and *n*-BuLi (1.26 mmol). Purification by flash chromatography (7:3 hexanes–AcOEt) afforded the pure oxazolidinone **6d** (180 mg, 55%); mp 100°C (Et_2O–hexanes); $[\alpha]_D^{22}$ +86.2 (*c* 0.5, $CHCl_3$); IR (KBr) 1792, 1711; ^1H NMR δ 0.86, 0.87 (2 d, $J=7$ Hz, 6H), 2.33 (m, 1H), 4.31 (m, 3H), 5.44, 5.52 (2d, $J=18.4$ Hz, 2H), 6.57 (d, $J=3$ Hz, 1H), 7.09–7.25 (m, 4H), 7.63 (dm, $J=7.8$ Hz, 1H); ^{13}C NMR δ 14.6 (CH_3), 17.7 (CH_3), 28.1 (CH), 49.4 (CH_2), 58.5 (CH), 64.3 (CH_2), 102.5 (CH), 108.8 (CH), 119.8 (CH), 121.1 (CH), 121.9 (CH), 128.5 (C), 128.7 (CH), 136.6 (C), 154.3 (C), 167.9 (C). Anal. calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.33; N, 9.78. Found: C, 67.01; H, 6.31; N, 9.75%.

4.6. (*S*)-*N*-(1-Indolyl)acetylprolinol 6e

Pivaloyl chloride (0.35 mL, 2.86 mmol) was slowly added to a solution of 1-indoleacetic acid (0.5 g, 2.86 mmol) and triethylamine (0.44 mL, 3.14 mmol) in THF (20 mL) cooled at 0°C, and the resulting whitish suspension was stirred at 0°C for 1 h. (*S*)-Prolinol (0.28 mL, 2.86 mmol) was added and the resulting solution was stirred at rt for 30 min. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. Evaporation of the dried organic extracts followed by flash chromatography (97:3 AcOEt–MeOH) afforded **6e** (0.66 g, 90%); mp 100°C (Et_2O–CH_2Cl_2); $[\alpha]_D^{22}$ −49 (*c* 1, $CHCl_3$); IR (KBr) 3429, 1632; ^1H NMR δ 1.57 (m, 1H), 1.80–1.99 (m, 3H), 3.30 (m, 1H), 3.39 (m, 1H), 3.59 (m, 2H), 4.15, 4.47 (2m, 2H), 4.77 (s, 2H), 6.55 (d, $J=3.3$ Hz, 1H), 7.06–7.22 (m, 4H), 7.63 (d, $J=7.8$ Hz, 1H); ^{13}C NMR δ 24.4 (CH_2), 27.7 (CH_2), 47.2 (CH_2), 49.0 (CH_2), 61.8 (CH), 66.2 (CH_2), 102.3 (CH), 108.9 (CH), 119.7 (CH), 121.1 (CH), 121.9 (CH), 128.4 (CH), 129.0 (C), 136.4 (C), 168.2 (C). Anal. calcd for $C_{15}H_{18}N_2O_2 \cdot 1/10H_2O$: C, 69.26; H, 7.05; N, 10.77. Found: C, 69.11; H, 7.15; N, 10.84%.

4.7. (*S*)-*N*-(1-Indolyl)acetyl-2-(methoxymethyl)-pyrrolidine 6f

A solution of prolinol **6e** (1 g, 3.8 mmol) in THF (40 mL) was added to a suspension of NaH (60%, 0.34 g, 8.57 mmol) in THF (10 mL) at 0°C, and the resulting suspension was stirred for 30 min at 0°C. MeI (1.5 mL, 14 mmol) was added and the reaction mixture was stirred at rt for 2 h. The mixture was poured into H_2O and extracted with Et_2O. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (flash, 3:7 hexanes–AcOEt) to afford **6f** (0.87 g, 83%, 3:2 mixture of rotamers); mp 72°C (Et_2O–hexane); $[\alpha]_D^{22}$ −39.3 (*c* 1, $CHCl_3$); IR (film) 1655; ^1H NMR δ 1.80–2.0 (m, 4H), 3.28 (s, 3H), 3.30 (m, 1H), 3.45 (m, 3H), 4.15, 4.21 (2m, 1H), 4.73 (s, NCH_2), 4.85, 5.15 (2d, $J=15$ Hz, NCH_2), 6.52 (d, $J=3$ Hz, 1H), 7.07–7.30 (m, 4H), 5.59 (d, $J=7.5$ Hz, 1H); ^{13}C NMR (major rotamer) δ 24.1 (CH_2), 26.9 (CH_2), 46.5 (CH_2), 48.9 (CH_2), 57.0 (CH), 58.7 (CH_3), 71.8 (CH_2), 101.8 (CH), 108.9 (CH), 119.4 (CH), 120.6 (CH), 121.6 (CH), 128.5 (CH), 128.7 (C), 136.4 (C), 165.9 (C); ^{13}C NMR δ (minor rotamer, most significant signals) 21.5 (CH_2), 28.6 (CH_2), 45.5 (CH_2), 48.3 (CH_2), 56.5 (CH), 58.9 (CH_3), 74.9 (CH_2). Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.28. Found: C, 70.41; H, 7.45; N, 10.12%.

4.8. 2-Iodoethyl acetate

Sodium iodide (9 g, 60 mmol) was added to a solution of 2-bromoethyl acetate (5 g, 29.9 mmol) in anhydrous acetone (50 mL) and the resulting mixture was stirred at rt overnight. The reaction mixture was filtered and concentrated. The resulting residue was dissolved in AcOEt and washed with H_2O. The solvent was removed, and the crude residue (5.4 g, 87%) was used directly in the next reaction.

4.9. 1-(2-Acetoxyethyl)-3-[(*E*)-2-(methoxycarbonyl)-vinyl]pyridinium iodide 7

A mixture of methyl (*E*)-3-(3-pyridyl)acrylate (6.4 g, 39 mmol) and 2-acetoxyethyl iodide (10 g, 46 mmol) was heated at 90–100°C for 2 h. The mixture was diluted with Et_2O, and the resulting precipitate was filtered to afford pyridinium iodide **7** (13.2 g, 90%); mp 161–163°C (acetone–MeOH); ^1H NMR (DMSO-d_6) δ 2.03 (s, 3H), 3.84 (s, 3H), 4.62 (t, $J=5.1$ Hz, 2H), 4.92 (t, $J=5.1$ Hz, 2H), 7.14 (d, $J=16.2$ Hz, 1H), 7.85 (d, $J=16.2$ Hz, 1H), 8.29 (dd, $J=8$, 6.1 Hz, 1H), 9.03 (d, $J=8$ Hz, 1H), 9.14 (d, $J=6.1$ Hz, 1H), 9.59 (s, 1H). Anal. calcd for $C_{13}H_{16}NO_4I \cdot H_2O$: C, 39.51; H, 4.59; N, 3.54. Found: C, 39.55; H, 4.19; N, 3.54%.

4.10. (1*R*,3*R*,4*S*)-Menthyl (1*R**,2*S**,6*S**)-5-(2-acetoxyethyl)-3-[(*E*)-2-(methoxycarbonyl)vinyl]-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1-carboxylate 8a

LHMDS (1.7 mmol) was added to a solution of ester **6a** (0.5 g, 1.6 mmol) in THF (40 mL) cooled at −78°C, and the resulting solution was stirred at −78°C for 45 min. Pyridinium iodide **7** (0.6 g, 1.6 mmol) was added in portions, and the mixture was allowed to rise to −30°C and stirred at this temperature for 1.5 h. A saturated C_6H_6 solution of dry HCl was added dropwise to bring the pH to 3.5–4, and the reaction mixture was heated at 60°C for 2 h. The reaction mixture was poured into a saturated aqueous Na_2CO_3 solution and extracted with Et_2O. Evaporation of the ethereal extracts followed by flash chromatography (hexanes–AcOEt, increasing polarity) afforded tetracycles **8a** (353 mg, 40%, 1:1 diastereomeric mixture); IR (film) 1741; ^1H NMR (most significant signals from the mixture) δ 0.45, 0.65, 0.75, 0.88, 0.95 (5d, $J=6.5$ Hz, 9H), 2.07 (s, 3H), 3.30 (br s, 1H), 3.70 (s, 3H), 4.10, 4.25 (m, 2H), 4.60 (br s, 1H), 4.70 (m, 1H), 5.05, 5.15 (2s, 1H, 16-H), 5.70, 5.75 (2d, $J=15$ Hz, 1H), 6.40 (s, 2H), 7.0–7.4 (m, 4H), 7.50 (d, $J=8$ Hz, 1H); ^{13}C NMR δ 15.4, 16.2 (CH_3), 20.5 (CH_3), 21.6 (CH_3), 21.8 (CH_3), 22.6 (CH_2), 23.4 (CH_2), 25.4, 26.5 (CH), 28.9, 29.1 (CH), 31.2 (CH), 33.9 (CH_2), 40.4, 40.5 (CH_2), 46.5, 46.6 (CH), 48.5 (CH), 50.8

(CH_3), 51.7 (CH_2), 59.2, 59.7 (CH), 61.5, 61.6 (CH_2), 75.8, 75.9 (CH), 99.3 (CH), 104.0 (CH), 105.9 (C), 109.0 (CH), 120.2, 120.3 (CH), 120.6, 120.7 (CH), 122.0, 122.1 (CH), 127.6 (C), 134.6, 134.7 (C), 136.5 (C), 144.1 (CH), 144.9 (CH), 168.7, 169.3, 169.7, 170.4 (CO). Anal. calcd for $C_{33}H_{42}N_2O_6 \cdot 1/3CH_2Cl_2$: C, 67.61; H, 7.26; N, 4.73. Found: C, 67.27; H, 7.26; N, 4.80%.

4.11. Reaction of ester 6b with pyridinium iodide 7

Method A. Ester **6b** (0.65 g, 1.67 mmol) in anhydrous THF (45 mL) was allowed to react with LHMDS (1.84 mmol) and then with pyridinium iodide **7** (0.63 g, 1.67 mmol) as described above. After workup, the crude residue was chromatographed. Elution with 8:2 hexanes–Et_2O afforded (1*R*,3*R*,4*S*)-8-phenylmenthyl (1*R**,2*S**,6*S**)-5-(2-acetoxyethyl)-3-[(*E*)-2-(methoxycarbonyl)vinyl]-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1-carboxylate **8b** (300 mg, 28%. 2.5:1 diastereomeric mixture); IR (film): 1742, 1702, 1584; ^{1}H NMR (major isomer, assignment aided by HMQC) δ 0.82 (m, 1H, 6′-H), 0.85 (d, $J=6.5$ Hz, 3H, CH_3), 0.94 (m, 1H, 2′-H), 1.30, 1.44 (2s, 6H, CH_3), 1.42 (m, 1H, 1′-H), 1.59 (m, 1H, 6′-H), 1.91 (m, 1H, 2′-H), 1.94 (m, 1H, 14-H) 2.07 (s, 3H, MeCO), 2.11 (1H, 4′-H), 2.23 (dm, $J=15$ Hz, 1H, 14-H), 3.21 (m, 2H, 5-H), 3.81 (s, 3H, OMe), 4.12, 4.44 (2m, 2H, 6-H), 4.56 (br s, 1H, 3-H), 4.67 (s, 1H, 16-H), 4.90 (m, 1H, 3′-H), 5.66 (d, $J=15$ Hz, 1H, 18-H), 6.39 (s, 1H, 7-H), 6.41 (s, 1H, 21-H), 6.99–7.42 (m, 8H, Ar), 7.56 (d, $J=8$ Hz, 1H, 9-H); ^{1}H NMR (minor isomer) δ 4.90 (s, 1H, 16-H), 5.57 (d, $J=15$ Hz, 1H, 18-H); ^{13}C NMR (major isomer, assignment aided by HMQC) δ 20.8 (MeCO), 21.7, 25.6, 28.3 (C-7′, C-9′, C-10′), 22.9 (C-14), 26.9 (C-5′), 31.2 (C-1′), 34.3 (C-6′), 40.2 (C-8′), 41.5 (C-2′), 48.6 (C-3), 49.9 (C-4′), 51.1 (OMe), 51.8 (C-5), 59.4 (C-16), 61.7 (C-6), 75.2 (C-3′), 99.5 (C-7), 104.5 (C-18), 106.0 (C-20), 109.6 (C-12), 120.4 (C-9), 120.8 (C-10), 122.1 (C-11), 125.1, 128.1 (Ph), 134.6 (C-2), 136.8 (C-13), 150.7 (Ph), 144.3 (C-21), 145.1 (C-19), 168.9, 169.6, 170.7 (CO). Anal. calcd for $C_{39}H_{48}N_2O_6$: C, 73.33; H, 7.26; N, 4.40. Found: C, 73.28; H, 7.25; N, 4.33%. On elution with 97:3 Et_2O–MeOH the deacetyl derivatives **9b** were obtained (93 mg, 9%. 1:1 diastereomeric mixture); IR (film) 3400, 1740, 1702, 1580; ^{1}H NMR (most significant signals from the mixture) δ 0.85 (d, $J=6.5$ Hz, 3H), 1.33, 1.45 (2s, 6H), 2.88, 3.26 (2 br s, 1H), 3.10, 3.48 (2 m), 3.70 (m, 2H), 3.76, 3.80 (2s, 6H), 4.59 (br s, 1H), 4.67, 4.90 (2s, 1H, 16-H), 4.85 (m, 1H), 5.53, 5.65 (2d, $J=15$ Hz, 1H), 6.38 (s, 1H), 6.44, 6.47 (2s, 1H), 6.96–7.42 (m, 8H), 7.53, 7.55 (2d, $J=8$ Hz, 1H); ^{13}C NMR (from the mixture) δ 21.7 (CH_3), 22.9, 23.0 (CH_2), 25.2, 25.5 (CH_3), 26.8, 27.1 (CH_2), 27.1, 27.6 (CH), 27.6, 28.3 (CH_3), 31.2, 31.3 (CH), 34.3 (CH_2), 40.1 (C), 41.4, 42.0 (CH_2), 48.9 (CH), 49.7, 49.8 (CH), 51.1 (CH_3), 55.4 (CH_2), 59.4, 59.7 (CH), 60.6 (CH_2), 75.5, 76.7 (CH), 99.3, 99.4 (CH), 103.6 (CH), 105.5 (C), 109.3, 109.5 (CH), 120.3, 120.4 (CH), 120.8 (CH), 122.0, 122.1 (CH), 125.4 (CH), 125.5 (CH), 127.9 (C), 128.1 (CH), 135.1, 135.0 (C), 136.6, 136.7 (C), 144.9 (CH), 145.4 (CH), 150.4, 150.6 (C), 169.2 (C), 169.7 (C).

Method B. Operating as above, but using LDA as the base, tetracycles **8b** (2:1 diastereomeric mixture, 28%) and **9b** (1:1 diastereomeric mixture, 21%) were obtained.

4.12. (1*R*,3*R*,4*S*)-Menthyl (1*R**,2*S**,6*S**)-(3*E*)-ethylidene-5-(2-hydroxyethyl)-1,2,5,6-tetrahydro-2,6-methano-[1,4]diazocino-[1,2-*a*]indole-1-carboxylate 10a

A suspension of tetracycles **8a** (1:1 diastereomeric mixture, 0.5 g, 0.88 mmol) in MeOH (12 mL) and aqueous HCl (4N, 36 mL) was refluxed for 2 h and then concentrated. The residue was dissolved in a methanolic solution of dry HCl (1.5N, 60 mL) and stirred at rt overnight. The solvent was removed, and the residue was dissolved in MeOH (45 mL), treated with $NaBH_4$ (120 mg, 3.6 mmol) at 0°C, and stirred at this temperature for 1 h. The solvent was removed, and the residue was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated, and the resultant residue was chromatographed (1:1 hexanes–AcOEt) to give tetracycles **10a** (115 mg, 28%. 1:1 diastereomeric mixture); IR (KBr) 1738; ^{1}H NMR (from the mixture, assignment aided by HMQC) δ 0.50, 0.59, 0.75, 0.86, 0.92 (5d, $J=6.5$ Hz, 9H, $3CH_3$), 0.90 (masked, 2H, 2′-H and 6′-H), 1.05 (m, 1H, 4′-H), 1.20 (m, 1H, 8′-H), 1.45 (m, 1H, 1′-H), 1.70 (m, 3H, 5′-H and 6′-H), 1.78 (dd, $J=6.9$ Hz, 3H, 18-H), 1.90 (m, 1H, 2′-H), 2.05 (dt, $J=14$, 3 Hz, 1H, 14-H), 2.35 (m, 2H, 5-H and 14-H), 2.55 (m, 1H, 21-H), 2.80 (m, 1H, 5-H), 3.05 (d, $J=15$ Hz, 1H, 21-H), 3.45 (br s, 1H, 15-H), 3.65 (m, 2H, 6-H), 4.05 (br s, 1H, 3-H), 4.60, 4.65 (2td, $J=11$, 3 Hz, 1H, 3′-H), 4.80 and 4.82 (2s, 1H, 16-H), 5.43 (br q, $J=6.9$ Hz, 1H, 18-H), 6.31, 6.32 (2s, 1H, 7-H), 7.05–7.20 (m, 3H), 7.60 (m, 1H, 9-H); ^{13}C NMR (assignment aided by HMQC) δ 12.5 (C-18), 15.4, 16.1 (C-7′), 20.6, 20.7, 21.9 (C-9′, C-10′), 22.6, 23.1 (C-5′), 25.0, 26.4 (C-8′), 27.6 (C-14), 31.2, 31.3 (C-15), 31.6 (C-1′), 34.0, 34.1 (C-6′), 40.4, 40.5 (C-2′), 46.6, 46.7 (C-4′), 51.6, 51.7 (C-3), 54.2 (C-21), 56.3 (C-5), 57.7 (C-6), 59.8, 60.0 (C-16), 75.6, 75.9 (C-3′), 101.1 (C-7), 108.6 (C-12), 120.1-121.5 (indole, C-19), 127.9 (C-8), 132.0, 135.1, 136.0 (C-2, C-13, C-20), 170.0, 170.2 (CO); HRMS calcd for $C_{29}H_{40}N_2O_2$ 464.3038, found 464.3048.

4.13. (1*R*,3*R*,4*S*)-8-Phenylmenthyl (1*R**,2*S**,6*S**)-3(*E*)-ethylidene-5-(2-hydroxyethyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1-carboxylate 10b

Operating as above, from tetracycles **8b** (2.5:1 diastereomeric mixture, 0.22 g, 0.36 mmol) afforded the ethylidene derivatives **10b** (58 mg, 30%, 2.5:1 diastereomeric mixture) after flash chromatography (AcOEt); IR (film) 3400, 1744; ^{1}H NMR (from the mixture, assignment aided by HMQC) δ 0.85 (d, $J=6.5$ Hz, 3H, CH_3), 1.01 (2m, 2H, 2′-H and 6′-H), 1.25, 1.38 (2s, 6H, CH_3), 1.45 (m, 1H, 1′-H), 1.65 (dm, 1H, 6′-H), 1.75 (2dd, $J=6.8$ Hz, 3H, 18-H), 1.90 (m, 3H, 4′-H and 2′-H), 2.05 (dm, $J=15$ Hz, 1H, 14-H), 2.33 (m, 1H, 14-H), 2.42 (dm, $J=12.5$ Hz, 1H, 21-H), 2.58, 2.80 (2m, 2H, 5-H), 2.96 (d, $J=12.5$ Hz, 1H, 21-H),

3.39, 3.45 (2 br s, 1H, 15-H), 3.63 (m, 2H, 6-H), 4.02, 4.12 (2t, 1H, 3-H), 4.22, 4.79 (2s, 1H, 16-H), 4.80 (m, 1H, 3′-H), 5.49 (m, 1H, 19-H), 6.30 (s, 1H, 7-H), 7.01–7.65 (m, 9H, Ar); ^{13}C NMR (major diastereomer, assignment aided by HMQC) δ 12.7 (C-18), 21.7, 26.1 27.7 (C-7′, C-9′, C-10′), 26.7 (C-5′), 27.6 (C-14), 31.3 (C-1′, C-15), 34.2 (C-6′), 39.7 (C-8′), 41.3 (C-2′), 50.1 (C-4′), 51.8 (C-3), 54.2 (C-5), 56.3 (C-21), 57.7 (C-6), 59.7 (C-16), 77.6 (C-3′), 101.4 (C-7), 109.2 (C-12), 120.1, 120.6, 121.3, 121.5 (indole, C-19), 125.3–128.1 (Ph), 128.6 (C-8), 131.8, 134.9, 137.4 (C-2, C-13, C-20), 151.3 (Ph), 169.1 (CO); HRMS calcd for $C_{35}H_{44}N_2O_3$ 540.3351, found 540.3353.

4.14. Methyl (1*R**,2*S**,6*S**)-5-(2-acetoxyethyl)-1-[(4*S*)-benzyl-2-oxo-1,3-oxazolidinylcarbonyl]-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-(3*E*)-acrylate 8c

Oxazolidinone **6c** (0.3 g, 0.89 mmol) was allowed to react with LDA (0.97 mmol) in THF (30 mL) at −78°C for 30 min, and then with pyridinium iodide **7** (0.34 g, 0.89 mmol) as described for the preparation of tetracycles **8a**. After the usual workup, the resulting residue was chromatographed. Elution with 1:1 hexanes–AcOEt afforded tetracycle **8c** (62 mg, 12%, minor diastereomer); mp 166°C (Et_2O–hexanes); $[\alpha]_D^{22}$ +508 (*c* 1, $CHCl_3$), +471 (*c* 0.5, acetone); IR (KBr) 1778, 1736, 1698, 1581; ms, *m*/*z* (rel. intensity) 583 (M^+, 18), 379 (100); ^{1}H NMR (500 MHz, assignment aided by NOESY and HMQC) δ 1.86 (dt, *J*=13, 3.2 Hz, 1H, 14-H), 2.07 (s, 3H, COMe), 2.47 (dt, *J*=13, 2.7 Hz, 1H, 14-H), 2.73 (dd, *J*=13.2, 9.5 Hz, 1H, CH_2Ph), 3.18 (m, 1H, 15-H), 3.20 (m, 2H, CH_2Ph and 5-H), 3.59 (dt, *J*=15, 4.1 Hz, 1H, 5-H), 3.73 (s, 3H, OMe), 4.12 (m, 1H, 6-H), 4.26 (m, 2H, 5′-H), 4.15 (m, 1H, 6-H), 4.60 (br s, 1H, 3-H), 4.63 (m, 1H, 4′-H), 5.98 (d, *J*=15.4 Hz, 1H, 18-H), 6.44, 6.45 (2s, 2H, 21-H, 7-H), 6.53 (d, *J*=1.6 Hz, 1H, 16-H), 7.06–7.32 (m, 9H, Ar, 19-H), 7.57 (dm, *J*=8 Hz, 1H, 9-H); ^{13}C NMR (assignment aided by HMQC) δ 20.8 (MeCO), 21.9 (C-14), 28.8 (C-15), 38.3 (CH_2Ph), 48.7 (C-3), 51.0 (OMe), 51.5 (C-5), 54.8 (C-4′), 58.5 (C-16), 61.8 (C-6), 67.3 (C-5′), 99.8 (C-7), 105.3 (C-20), 105.4 (C-18), 108.9 (C-12), 120.7 (C-9), 121.0 (C-10), 122.5 (C-11), 128.1 (C-8), 127.5, 128.1, 128.9, 134.5 (Ph), 135.5 (C-2), 144.9 (C-21), 145.3 (C-19), 153.2, 169.3, 170.6 (CO), 170.7 (CO). Anal. calcd for $C_{33}H_{33}N_3O_7$: C, 67.91; H, 5.69; N, 7.20. Found: C, 67.80; H, 5.76; N, 7.13%. Elution with 4:6 hexane–AcOEt afforded tetracycle **8c** (93 mg, 18%, major diastereomer); $[\alpha]_D^{22}$ −539 (*c* 1, $CHCl_3$), −387.6 (*c* 0.5, acetone); IR (KBr) 1778, 1737, 1696, 1578; ms, *m*/*z* (rel. intensity) 583 (M^+, 15), 379 (100); ^{1}H NMR (500 MHz, assignment aided by NOESY and HMQC) δ 1.91 (dt, *J*=13, 3.5 Hz, 1H, 14-H), 2.09 (s, 3H, COMe), 2.64 (dt, *J*=13, 2.5 Hz, 1H, 14-H), 2.70 (dd, *J*=13.5, 9.5 Hz, 1H, CH_2Ph), 3.02 (dd, *J*=14, 2.5 Hz, 1H, CH_2Ph), 3.20 (br s, 1H, 15-H), 3.24 (m, 1H, 5-H), 3.64 (dt, *J*=15, 4.4 Hz, 1H, 5-H), 3.71 (s, 3H, OMe), 4.15 (m, 1H, 6-H), 4.30 (m, 2H, 5′-H), 4.40 (m, 1H, 6-H), 4.57 (m, 1H, 4′-H), 4.64 (br s, 1H, 3-H), 5.87 (d, *J*=15.4 Hz, 1H, 18-H), 6.46 (s, 1H, 21-H), 6.48 (s, 1H, 7-H), 6.58 (d, *J*=1.3 Hz, 1H, 16-H), 7.06–7.28 (m, 9H, Ar, 19-H), 7.59 (d, *J*=7.5 Hz, 1H, 9-H); ^{13}C NMR (assignment aided by HMQC) δ 20.8 (COMe), 22.0 (C-14), 28.8 (C-15), 37.1 (CH_2Ph), 48.7 (C-3), 51.1 (OMe), 51.5 (C-5), 56.2 (C-4), 58.2 (C-16), 61.8 (C-6), 66.6 (C-5′), 99.7 (C-7), 105.1 (C-18), 105.4 (C-20), 109.1 (C-12), 120.7 (C-9), 121.0 (C-10), 122.4 (C-11), 128.0 (C-8), 127.3, 128.8, 129.4, 134.5 (Ph), 135.5 (C-2), 137.0 (C-13), 144.9 (C-21), 145.3 (C-19), 152.9, 169.2, 170.7 (CO). Anal. calcd for $C_{33}H_{33}N_3O_7\cdot H_2O$: C, 65.88; H, 5.86; N, 6.98. Found: C, 65.82; H, 5.77; N, 7.00%.

4.15. Methyl (1*R**,2*S**,6*S**)-5-(2-acetoxyethyl)-1-[(4*S*)-isopropyl-2-oxo-1,3-oxazolidinylcarbonyl]-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-(3*E*)-acrylate 8d

Operating as in the preparation of tetracycles **8a**, from oxazolidinone **6d** (0.37 g, 1.3 mmol), and pyridinium iodide **7** (0.49 g, 1.29 mmol), a residue was obtained and then chromatographed. Elution with 1:1 hexanes–AcOEt afforded tetracycle **8d** (70 mg, 13%, minor diastereomer); mp 158°C (Et_2O–hexanes); $[\alpha]_D^{22}$ +849 (*c* 0.5, $CHCl_3$); IR (KBr) 1777, 1737, 1698, 1582; ^{1}H NMR δ 0.87, 0.93 (2d, *J*=6.8 Hz, 6H), 1.90 (dt, *J*=13.1, 3.3 Hz, 1H), 2.08 (s, 3H), 2.25 (m, 1H), 2.45 (dt, *J*=13.1, 2.5 Hz, 1H), 3.20 (m, 1H), 3.25 (br s, 1H), 3.61 (dt, *J*=16, 4.5 Hz, 1H), 3.74 (s, 3H), 4.11 (m, 1H), 4.39 (m, 4H), 4.60 (br s, 1H), 6.05 (d, *J*=15 Hz, 1H), 6.44, 6.46 (2s, 2H), 6.56 (s, 1H, 16-H), 7.10–7.26 (m, 4H), 7.60 (d, *J*=7.8 Hz, 1H); ^{13}C NMR δ 15.0, 17.7 (CH_3), 20.8 (CH_3), 21.9 (CH_2), 28.4 (CH), 29.2 (CH), 48.7 (CH), 51.1 (CH_3), 51.6 (CH_2), 58.2 (CH), 58.9 (CH), 61.7 (CH_2), 64.2 (CH_2), 99.8 (CH), 105.4 (CH), 105.5 (C), 109.7 (CH), 120.7 (CH), 121.0 (CH), 122.5 (CH), 128.1 (C), 135.4 (C), 137.3 (C), 144.9 (CH), 145.4 (CH), 153.7, 169.4, 170.5 (C). Anal. calcd for $C_{29}H_{33}N_3O_7\cdot 1/2H_2O$: C, 63.96; H, 6.29; N, 7.72. Found: C, 64.03; H, 6.65; N, 7.43%. Elution with 4:6 hexane–AcOEt afforded tetracycle **8d** (98 mg, 18%, major diastereomer); mp 195°C (Et_2O–hexanes); $[\alpha]_D^{22}$ −962 (*c* 0.5, $CHCl_3$); IR (film) 1778, 1738, 1697, 1582; ^{1}H NMR (assignment aided by HMQC) δ 0.75, 0.80 (2d, *J*=7 Hz, 6H, CH_3), 1.86 (dt, *J*=13, 3 Hz, 1H, 14-H), 2.06 (s, 3H, COMe), 2.11 (m, 1H, CH), 2.61 (dt, *J*=13, 2.4 Hz, 1H, 14-H), 3.20 (m, 2H, 15-H, 5-H), 3.60 (dt, *J*=15, 4 Hz, 1H, 5-H), 3.72 (s, 3H, OMe), 4.11 (m, 1H, 6-H), 4.35 (m, 4H, 4′-H, 5′-H, 6-H), 4.60 (br s, 1H, 3-H), 5.94 (d, *J*=15 Hz, 1H, 18-H), 6.43, 6.46 (2s, 2H, 21-H, 7-H), 6.57 (s, 1H, 16-H), 7.06–7.25 (m, 4H, indole, 19-H), 7.55 (d, *J*=7.8 Hz, 1H, 9-H); ^{13}C NMR (assignment aided by HMQC) δ 14.1, 17.7 (Me), 20.8 (MeCO), 21.9 (C-14), 27.6 (CH), 28.5 (C-15), 48.7 (C-3), 51.0 (OMe), 51.5 (C-5), 58.1 (C-16), 59.2 (C-4′), 61.7 (C-6), 63.6 (C-5′), 99.6 (C-7), 105.3 (C-18), 105.5 (C-20), 109.0 (C-12), 120.7 (C-9), 121.0 (C-10), 122.3 (C-11), 128.1 (C-8), 135.5 (C-2), 136.9 (C-13), 144.9 (C-21), 145.4 (C-19), 156.6, 169.3, 170.4, 170.7 (CO).

4.16. Methyl (1*R**,2*S**,6*S**)-5-(2-hydroxyethyl)-1-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]-diazocino[1,2-*a*]indole-(3*E*)-acrylate 11[3a]

Aqueous hydrogen peroxide (33%, 0.2 mL, 1.76 mmol) and $LiOH·H_2O$ (0.024 g, 0.55 mmol) were added to a solution of tetracycle **8c** (major diastereomer, 0.1 g, 0.17 mmol) in THF (3 mL) and H_2O (1 mL), cooled at 0°C, and the resulting mixture was stirred at 0°C for 45 min. The reaction mixture was poured into an aqueous Na_2SO_3 solution, acidified with aqueous HCl (4N) and extracted with AcOEt. The organic extracts were dried and concentrated. The resulting residue was dissolved in a methanolic solution of dry HCl (1.5N, 20 mL) and stirred at rt for 15 h. The solvent was removed and the residue was partitioned between a saturated aqueous Na_2CO_3 solution and Et_2O, and extracted with Et_2O. The organic extracts were dried and concentrated and the residue was chromatographed (flash, 1:1 Et_2O–CH_2Cl_2). Initial elution gave (*S*)-4-benzyl-2-oxazolidinone (17 mg, 56%). Further elution gave tetracycle (−)-**11** (4 mg, 5%); $[\alpha]_D^{22}$ −285 (*c* 0.15, $CHCl_3$). Similarly, starting from tetracycle **8c** (minor diastereomer, 0.1 g, 0.17 mmol) tetracycle (+)-**11** was obtained: 4 mg (5%); $[\alpha]_D^{22}$ +300 (*c* 0.17, $CHCl_3$).

4.17. Methyl (1*R**,2*S**,6*S**)-5-(2-acetoxyethyl)-1-[(2*S*)-(hydroxymethyl)pyrrolidinylcarbonyl]-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-(3*E*)-acrylate 8e

A solution of amide **6e** (0.3 g, 1.16 mmol) in THF (10 mL) was added to a solution of LDA (2.4 mmol) in THF (6 mL) cooled at 0°C, and the mixture was stirred at 0°C for 1 h. The resulting solution was cooled at −60°C and pyridinium iodide **7** (0.44 g, 1.16 mmol) was added portionwise. The reaction mixture was allowed to rise to −40°C, HMPA (0.17 mL, 1.16 mmol) was added and the mixture was stirred at −40°C for 1.5 h, and then cooled again at −70°C. A saturated C_6H_6 solution of dry HCl was added to bring the pH to 3–4, and the mixture was stirred at rt for 4 h. The reaction mixture was poured into a 10% aqueous Na_2CO_3 solution and extracted with Et_2O. After concentration of the organic extracts the resulting residue was chromatographed. Elution with AcOEt afforded tetracycle (+)-**8e** (110 mg, 19%, major diastereomer); mp 107°C (Et_2O); $[\alpha]_D^{22}$ +608 (*c* 0.5, $CHCl_3$); IR (NaCl) 3432, 1738, 1694, 1640; ^{1}H NMR δ 1.73–2.15 (m, 4H), 1.87 (dt, J=12.9, 3.6 Hz, 1H), 2.07 (s, 3H), 2.90 (dm, J=12.9, 1H), 3.14 (br s, 1H), 3.20 (m, 1H), 3.46 (dd, J=8.5 and 6.3 Hz, 1H), 3.59–3.67 (m, 3H), 3.73 (s, 3H), 3.86 (m, 2H), 4.12 (m, 2H), 4.63 (br s, 1H), 5.14 (br s, 1H, 16-H), 5.52 (d, J=15.4 Hz, 1H), 6.39 (s, 1H), 6.43 (s, 1H), 6.99–7.26 (m, 4H), 7.57 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 20.8 (CH_3), 22.1 (CH_2), 24.8 (CH_2), 27.5 (CH), 28.1 (CH_2), 48.0 (CH_2), 48.9 (CH), 51.1 (CH_3), 51.7 (CH_2), 59.0 (CH), 61.9 (CH_2), 62.2 (CH), 66.0 (CH_2), 99.4 (CH), 103.1 (CH), 106.0 (C), 108.4 (CH), 120.0 (CH), 121.2 (CH), 122.4 (CH), 127.9 (C), 135.5 (C), 136.5 (C), 145.2 (CH), 146.1 (CH), 168.7 (C), 169.7 (C), 170.7 (C). Anal. calcd for $C_{28}H_{33}N_3O_6·H_2O$: C, 63.98; H, 6.71; N, 7.99. Found: C, 63.84; H, 6.45; N, 7.92. Elution with 95:5 AcOEt–MeOH afforded tetracycle **8e** (35 mg, 6%, minor diastereomer); ^{1}H NMR (most significant signals) δ 2.04 (s, 3H), 2.7 (m, 1H), 3.73 (s, 3H), 4.05 (br s, 1H), 5.23 (br s, 1H, 16-H), 5.76 (d, J=15 Hz, 1H), 6.28 (s, 1H), 6.32 (s, 1H), 6.88–7.26 (m, 4H), 7.47 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 20.8 (CH_3), 24.1 (CH_2), 24.6 (CH_2), 25.5 (CH), 27.6 (CH_2), 47.7 (CH_2), 50.5 (CH), 50.9 (CH_3), 53.0 (CH_2), 61.3 (CH), 61.5 (CH_2), 61.8 (CH), 65.1 (CH_2), 99.7 (CH), 104.6 (CH), 107.9 (CH), 108.6 (C), 120.4 (CH), 121.0 (CH), 121.1 (CH), 128.5 (C), 136.4 (2C), 141.5 (CH), 144.2 (CH), 168.3 (C), 169.9 (C), 170.6 (CO).

4.18. Methyl (1*R**,2*S**,6*S**)-5-(2-acetoxyethyl)-1-[(2*S*)-(methoxymethyl)pyrrolidinylcarbonyl]-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-(3*E*)-acrylate 8f

Indole **6f** (0.2 g, 0.73 mmol) in THF (7 mL) was allowed to react with LDA (0.80 mmol) in THF (4 mL) and then with pyridinium iodide **7** (0.27 g, 0.73 mmol) and HMPA (0.2 mL, 0.73 mmol) as described for the preparation of **8e**. After workup the resulting crude residue was chromatographed (flash, 4:6 hexanes–AcOEt) to give tetracycles **8f** (38 mg, 10%, 1:1 diastereomeric mixture); mp 130°C (Et_2O–hexanes); IR (film) 1741, 1696, 1646; ^{1}H NMR (most significant signals from the mixture) δ 2.07 (s, 3H), 3.15 (br s, 1H), 3.31 (s, 3H), 3.75 (s, 3H), 4.61 (br s, 1H), 5.09, 5.18 (2s, 1H, 16-H), 6.40 (s, 1H), 6.41 (s, 1H), 6.85–7.3 (m, 4H), 7.55 (d, J=7.5 Hz, 1H); ^{13}C NMR (from the mixture) δ 20.8 (CH_3) 21.9, 22.0 (CH_2), 25.3, 24.7 (CH_2), 26.9, 27.3 (CH_2), 28.8, 28.2 (CH), 47.7 (CH_2), 49.0, 48.9 (CH), 51.0 (CH_3), 51.7 (CH_2), 57.0 (CH), 57.6 (CH), 58.8, 59.0 (CH_3), 61.8 (CH_2), 71.9, 71.7 (CH_2), 99.2, 99.0 (CH), 103.2 (CH), 106.3, 106.4 (C), 108.6, 108.9 (CH), 120.3, 120.5 (CH), 121.0 (CH), 121.8, 122.0 (CH), 127.9, 128.0 (C), 135.6 (C), 136.4, 136.7 (C), 145.2 (CH), 146.1 (CH), 167.9, 167.6, 168.7, 168.0, 170.7 (C). Anal. calcd for $C_{29}H_{35}N_3O_6·H_2O$: C, 64.54; H, 6.81; N, 7.78. Found: C, 64.82; H, 6.59; N, 7.90%.

4.19. (*S*)-(2-Pyrrolidinyl)methyl (1*R*,2*S*,6*S*)-(3*E*)-ethylidene-5-(2-hydroxyethyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1-carboxylate 12

A suspension of tetracycle (+)-**8e** (major diastereomer, 60 mg, 0.12 mmol) in EtOH (2 mL) and aqueous HCl (4N, 5 mL) was heated under reflux for 2 h and then concentrated. The residue was dissolved in MeOH (5 mL), treated with $NaBH_4$ (40 mg, excess) at 0°C, and stirred at this temperature for 1 h. The solvent was removed, and the residue was partitioned between H_2O and Et_2O, and extracted with Et_2O. The organic extracts were dried and concentrated, and the residue was chromatographed (flash, 8:1:1 Et_2O–EtOH–DEA) to give **12** (15 mg, 33%); IR (KBr) 1736, 3300; ^{1}H NMR δ 1.62 (m, 4H), 1.80 (dd, J=6.9 and 2 Hz, 3H), 2.05–2.85 (m, 8H), 3.10 (m, 2H), 3.63 (m, 4H), 3.82 (dd, J=11 and 6.6 Hz, 1H), 4.07 (br s, 1H), 4.22 (dd, J=11 and 4.4 Hz, 1H), 4.86 (s, 1H, 16-H), 5.45 (q, J=6.9 Hz, 1H), 6.33 (s, 1H), 7.11–7.20 (m, 3H), 7.59 (d, J=8 Hz, 1H); ^{13}C NMR δ 12.9 (CH_3), 24.6 (CH_2), 27.6 (CH_2), 28.1 (CH_2), 29.6 (CH), 51.8 (CH), 54.6 (CH_2), 56.3

(CH_2), 56.3 (CH_2), 56.4 (CH_2), 57.3 (CH_2), 60.0 (CH), 62.1 (CH), 65.8 (CH_2), 101.3 (CH), 108.0 (CH), 120.4 (CH), 120.6 (CH), 120.9 (CH), 121.0 (CH), 127.7 (C), 135.5 (C), 135.6 (C), 136.5 (C), 169.9 (C); HRMS calcd for $C_{24}H_{31}N_3O_3$ 409.2365, found 409.2363.

4.20. (+)-16-Epivinoxine 13

A solution of CH_3MgBr in Et_2O (3 M, 0.4 mmol) was added to anhydrous MeOH at 0°C, and the mixture was stirred for 15 min at this temperature. The resulting suspension was added to a solution of tetracycle **12** (15 mg, 0.037 mmol) in MeOH (1 mL) and CH_2Cl_2 (1 mL) cooled at 0°C. The reaction mixture was heated under reflux for 2 h, quenched with H_2O, and extracted with CH_2Cl_2. The organic extracts were concentrated and the residue was purified by flash chromatography (8:1:1 Et_2O–EtOH–DEA) to give **13**: 6 mg (50%); $[\alpha]_D^{22}$ +109 (*c* 0.11, $CHCl_3$); CD (EtOH, $c=5$ mM) λ_{max} (nm) 227.8 ($\Delta\varepsilon$ −4.6), 269.4 ($\Delta\varepsilon$ +1.5), 298.6 ($\Delta\varepsilon$ +0.9).

4.21. Epimerization of (+)-16-epivinoxine 13

t-BuOK (0.5 g, 4.5 mmol) was added to a solution of **13** (0.023 g, 0.06 mmol) in MeOH (10 mL), and the resulting mixture was heated under reflux for 5 h. The suspension was cooled at 0°C, a solution of dry HCl in MeOH (5N) was added to bring the pH to 3–4, and the mixture was stirred at rt overnight. The solvent was removed and the resultant residue was diluted with a saturated aqueous Na_2CO_3 solution and extracted with Et_2O. The organic extracts were dried and concentrated to give a 2:1 (^1H NMR) mixture of (+)-epivinoxine **13** and (−)-vinoxine **1** (17 mg, 74%). After flash chromatography (25:1 AcOEt–MeOH) the ratio (+)-**13**/(−)-**1** of the mixture was shifted to 14:86 (HPLC): $[\alpha]_D^{22}$ +4 (*c* 0.1, $CHCl_3$), lit.[14b] for (−)-vinoxine $[\alpha]_D^{24}$ −18.6 (*c* not given, $CHCl_3$); CD (EtOH, $c=0.18$ mM) λ_{max} (nm) 223.6 ($\Delta\varepsilon$ −1.9), 266.4 ($\Delta\varepsilon$ +0.22), 297.4 ($\Delta\varepsilon$ +0.12).

Acknowledgements

Financial support from the 'Ministerio de Ciencia y Tecnología' (Spain, project BQU2000-0785) is gratefully acknowledged. We also thank the 'Comissionat per a Universitats i Recerca' (Generalitat de Catalunya) for Grant 2001SGR00084. One of us (Y.A.) also thanks the 'Ministerio de Educación, Cultura y Deporte' for a grant.

References

1. For a review, see: Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587–596.
2. For the pioneering use of this reactivity pattern for the construction of indoloquinolizidine alkaloids, see: Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271–1276; (b) Wenkert, E.; Angell, E. C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. S.; Shi, Y.-J.; Sultana, M.; Vankar, Y. D. *J. Org. Chem.* **1986**, *51*, 2995–3000.
3. (a) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156–1168; (b) Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. *J. Org. Chem.* **1993**, *58*, 7756–7767.
4. (a) Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 5089–5092; (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299–6312.
5. (a) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239–1251; (b) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Tetrahedron* **1999**, *55*, 3117–3128.
6. (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597–3609; (b) Bennasar, M.-L.; Vidal, B.; Kumar, R.; Lázaro, A.; Bosch, J. *Eur. J. Org. Chem.* **2000**, 3919–3925.
7. Bennasar, M.-L.; Jiménez, J.-M.; Vidal, B.; Sufi, B. A.; Bosch, J. *J. Org. Chem.* **1999**, *64*, 9605–9612.
8. For the synthesis of chiral non-racemic 1,2-dihydropyridines, see: (a) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: London, 1996; Vol. 2, pp. 251–294. For more recent work, see: (b) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182–8187; (c) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184–2185; (d) Comins, D. L.; Zhang, Y.-M.; Joseph, S. P. *Org. Lett.* **1999**, *1*, 657–659; (e) Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839–2842; (f) Kuethe J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855–857. See also: (g) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052–2057.
9. Oxazoline: (a) Meyers, A. I.; Natale, N. R.; Wettlaufer, D. G.; Rafii, S.; Clardy, J. *Tetrahedron Lett.* **1981**, *22*, 5123–5126; (b) Meyers, A. I.; Natale, N. R. *Heterocycles* **1982**, *18*, 13–19; (c) Meyers, A. I.; Oppenlaender, T. *J. Chem. Soc., Chem. Commun.* **1986**, 920–921; (d) Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989–1996. Aminal: (e) Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877–1888; (f) Raussou, S.; Gosmini, R.; Mangeney, P.; Alexakis, A.; Commerçon, M. *Tetrahedron Lett.* **1994**, *35*, 5433–5436. See also: (g) Rezgui, F.; Mangeney, P.; Alexakis, A. *Tetrahedron Lett.* **1999**, *40*, 6241–6244. $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$: (h) Davies, S. G.; Skerlj, R. T.; Whittaker, M. *Tetrahedron Lett.* **1990**, *31*, 3213–3216; (i) Beckett, R. P.; Burgess, V. A.; Davies, S. G.; Whittaker, M. *Tetrahedron Lett.* **1993**, *34*, 3617–3620. Amides derived from (*S*)-thiazolidine-2-thiones and (*S*)-oxazolidinones: (j) Yamada, S.; Ichikawa, M. *Tetrahedron Lett.* **1999**, *40*, 4231–4234; (k) Yamada, S.; Misono, T.; Ichikawa, M.; Morita, C. *Tetrahedron* **2001**, *57*, 8939–8949.
10. For the synthesis of chiral non-racemic tetracyclic structures related to *Strychnos* alkaloids, see: Amat, M.; Coll, M.-D.; Bosch, J. *Tetrahedron* **1995**, *51*, 10759–10770.
11. Bennasar, M.-L.; Zulaica, E.; Alonso, Y.; Mata, I.; Molins, E.; Bosch, J. *Chem. Commun.* **2001**, 1166–1167.
12. (a) Amann, R.; Spitzner, D. *Angew. Chem., Int. Ed.* **1991**, *30*, 1320–1321; (b) Amann, R.; Arnold, K.; Spitzner, D.; Majer, Z.; Snatzke, G. *Liebigs Ann.* **1996**, 349–355.

13. Mokry, J.; Kompis, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2523–2531.
14. (a) Voticky, Z.; Grossmann, E.; Tomko, J.; Massiot, G.; Ahond, A.; Potier, P. *Tetrahedron Lett.* **1974**, 3923–3926; (b) Voticky, Z.; Grossmann, E.; Potier, P. *Collect. Czech. Chem. Commun.* **1977**, *42*, 548–552.
15. Bosch, J.; Bennasar, M.-L.; Rubiralta, M. *An. Quím.* **1987**, *83C*, 66–69.
16. Wenkert, E.; Guo, M.; Pestchanker, M. J.; Shi, Y.-J.; Vankar, Y. D. *J. Org. Chem.* **1989**, *54*, 1166–1174 and references cited therein. See also Refs. 3–7.
17. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.
18. (a) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Pergamon: Oxford, 1996; Chapter 5; (b) Feringa, B. L.; Jansen, J. F. G. A. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 4, pp. 2104–2155.
19. Herrmann, R. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 9, pp. 5759–6001.
20. The 15-H/16-H *trans* relative configuration was assigned by NMR analysis. See Refs. 3a and 15.
21. Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025–5028.
22. (a) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953–964; (b) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475–497; (c) Jones, G. B. *Tetrahedron* **2001**, *57*, 7999–8016.
23. Frater, G. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 2, pp. 723–761.
24. Högberg, H.-E. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 2, pp. 791–915.
25. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
26. See, inter alia: (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; (b) Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, 2175–2178; (c) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750–5752; (d) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548–7549.
27. Evans, D. A.; Britton, T. C.; Ellmann, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6143.
28. Only complex reaction mixtures were obtained when diastereomers **8c** were treated with $Mg(OMe)_2$[28a] or MgBrOMe.[28b,c] (a) Evans, D. A.; Morrisey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348; (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397; (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151–7157.
29. (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236; (b) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137–3139; (c) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109–1127.
30. For an example of participation of these enolates in Michael additions, see: Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minabi, T. *Tetrahedron Lett.* **1986**, *27*, 959–962.