Extending the Scope of the [2+2] Cycloaddition of Dichloroketene to Chiral Enol Ethers: Synthesis of (–)-Detoxinine

Julien Ceccon, Jean-François Poisson,* Andrew E. Greene

Université Joseph Fourier de Grenoble, Chimie Recherche (LEDSS), 38041 Grenoble, France
Fax +33(4)76514494; E-mail: jean-francois.poisson@ujf-grenoble.fr

Received 25 March 2005

Abstract: Allylic oxidation of a known lactam, obtained by asymmetric [2+2] cycloaddition of dichloroketene to a chiral enol ether, followed by Beckmann ring expansion and dechlorination, affords a potential intermediate for the synthesis of various natural products. The usefulness of this intermediate is first demonstrated by an asymmetric synthesis of (–)-detoxinine.

Key words: allylic oxidation, asymmetric synthesis, cycloaddition, lactam, natural product

The [2+2] cycloaddition of dichloroketene to chiral enol ethers has already proven highly effective for the synthesis of several natural alkaloids,[1] including the simple azasugars (–)-2-epilentiginosine and (+)-lentiginosine.[1b] To demonstrate that this chemistry can also provide access to the more complex indolizidine and pyrrolizidine azasugars, we have selected for synthesis (+)-castanospermine (**1**), (–)-swainsonine (**2**), and (+)-australine (**3**), popular synthetic targets that are potent inhibitors of glycosidases and of potential use in cancer chemotherapy (Figure 1).[2] A common intermediate in our synthetic strategy appeared to offer also an approach to the unusual amino acid (–)-detoxinine (**4**),[3] the parent structure of the depsipeptide metabolites of the detoxin complex, which has been isolated from various strains of streptomyces and displays a unique detoxification effect in both plant and animal cells.[4] In this communication, we describe a non-chiral pool, stereoselective synthesis of (–)-detoxinine.

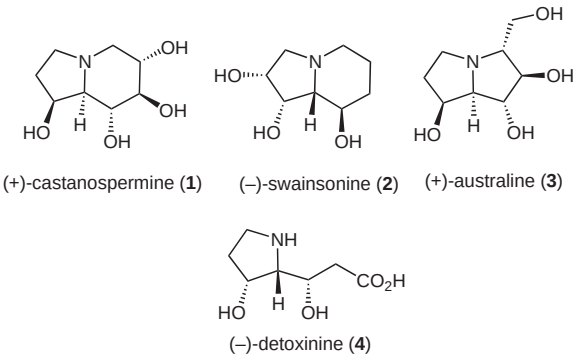
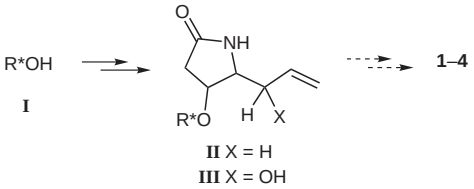


Figure 1

The pivotal intermediate in our program was anticipated to be allylic alcohol **III** (Scheme 1). Since a preparation of highly diastereomerically enriched lactam **II** from enantiopure 1-(2,4,6-triisopropylphenyl)ethanol was already available from previous work in our laboratory,[1a] its allylic oxidation to access **III** seemed worth examining, particularly in view of the encouraging literature precedent with SeO_2 on related systems.[5]

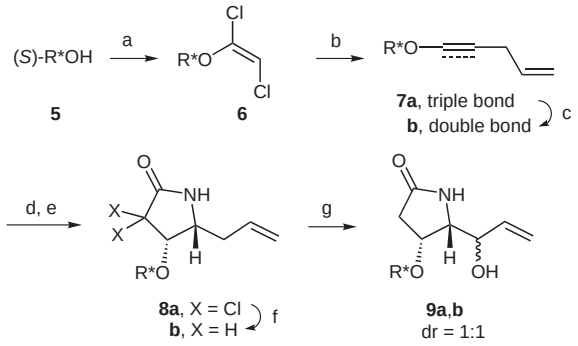


Scheme 1

Thus, lactam **8b** was synthesized as reported,[1a] with slight modification: The *S*-enantiomer of 1-(2,4,6-triisopropylphenyl)ethanol (**5**), chosen to gain access to the desired antipodal series, was converted in high yield to the dichloroenol ether **6**, which in turn was treated with 2 equivalents of *n*-BuLi, followed by allyl iodide, to yield ynol ether **7a** (Scheme 2). Partial reduction of the triple bond was performed with DIBAL-H in toluene at 50 °C,[6] instead of by catalytic hydrogenation with the Lindlar catalyst, to give enol ether **7b**, now free of the 10–20% of over-reduced material previously observed on hydrogenation.[1a] Diastereoface-selective cycloaddition of dichloroketene to **7b**, followed by Beckmann ring expansion and dechlorination, then afforded lactam **8b** in 38% overall yield for the five steps (82%/step). The diasteromeric purity of **8b** was found, as previously, to be excellent (ca. 95%, ^{1}H NMR); furthermore, the minor diastereomers, conveniently, filtered out over the subsequent steps of the synthesis.

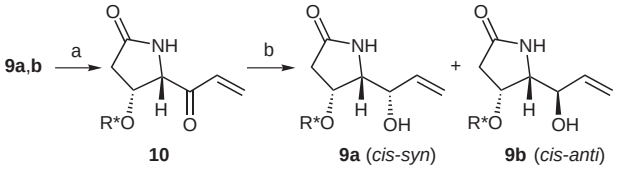
It was found that allylic oxidation of **8b** under Sharpless conditions (SeO_2, *t*-BuOOH, $ClCH_2CH_2Cl$, reflux) did indeed lead to the formation of the desired product, but initially in only 35% yield.[8] Optimization studies revealed that the corresponding enone was also formed, from oxidation of the allylic alcohol, and was unstable under the reaction conditions. Thus, the reaction was stopped before complete consumption of the starting lactam (3 h at 70 °C) and, in this way, lactams **9a**,**b** could be obtained in 56% yield (75%, based on recovered starting material).[9]

SYNLETT 2005, No. 9, pp 1413–1416
Advanced online publication: 29.04.2005
DOI: 10.1055/s-2005-868515; Art ID: G10505ST



Scheme 2 *Reagents and conditions*: a) KH, THF, 0 °C to 20 °C; trichloroethylene, –50 °C to 20 °C, 85%; b) *n*-BuLi, THF, –78 °C to –50 °C; allyl iodide, HMPA, –60 °C to 0 °C; c) DIBAL-H, THF, 50 °C; d) Cl_3CCOCl, Zn-Cu, Et_2O, 20 °C; e) $NH_2OSO_2C_6H_2(CH_3)_3$,[7] Na_2SO_4, CH_2Cl_2, 0 °C; Al_2O_3, MeOH; f) NH_4Cl, Zn-Cu, MeOH, 20 °C, 38% from **6** (82%/step); g) SeO_2, TBHP, $ClCH_2CH_2Cl$, 70 °C, 56% (75%, based on recovered starting material).[9] (*S*)-R*OH = (*S*)-1-(2,4,6-triisopropylphenyl)ethanol.

It was disappointing, however, to find that there was, essentially, a complete absence of stereoselectivity in this reaction. While the mixture could not readily be separated at this stage, it could be smoothly transformed in the presence of the Dess–Martin periodinane into the corresponding enone **10**, which could then be reduced (Scheme 3). The sensitive functionality in the enone limited, however, the range of possible reagents; the reducing reagents that were screened are listed in Table 1.



Scheme 3 *Reagents and conditions*: a) Dess–Martin periodinane, CH_2Cl_2; b) see Table 1.

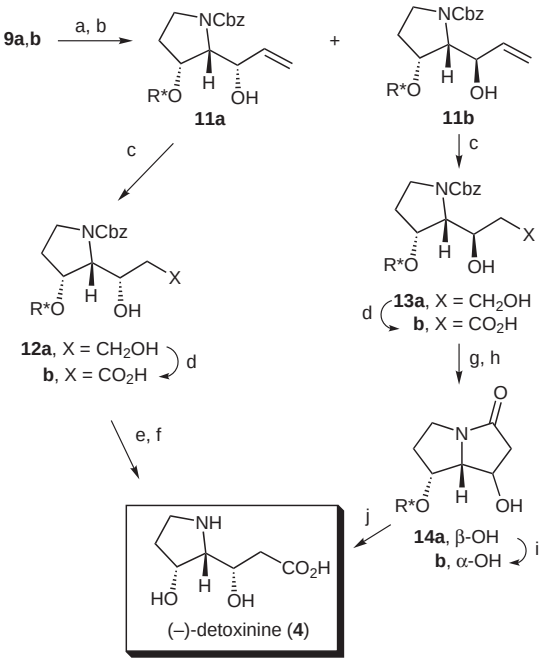
Table 1 Reduction of Enone **10**

Entry	Reagent	Conditions	dr (**9a**:**9b**)[a]	Yield (%)[b]
1	$NaBH_4$, $CeCl_3$	EtOH, 0 °C	1:5	83
2	$Zn(BH_4)_2$	Et_20, –78 °C to 20 °C	1:6	46
3	Red-Al	Toluene, 0 °C	1:8	43
4	$LiAlH_4$	THF, –15 °C	1:12	89
5	(+)-DIPCl	THF, 0 °C	1:2	<30
6	(–)-DIPCl	THF, 20 °C	N.R.	N.R.

[a] Determined by ^1H NMR.[10]
[b] Over two steps.

In all cases, the *cis-anti* isomer **9b** was the major product, ranging from 12:1, obtained through controlled $LiAlH_4$ reduction, to 2:1, secured by using the chiral reagent (+)-DIPCl.[10] The preference for the *cis-anti* isomer is consistent with a Felkin–Anh like reactive conformation, although chelation may also be involved (entries 3, 4). It is worth noting that lactam **9b**, although not the desired isomer in the present context, does possess the relative stereochemistry found in a large number of alkaloids (e.g., **1**–**3**) and, together with its enantiomer formed from (*R*)-1-(2,4,6-triisopropylphenyl)ethanol, should be quite useful for accessing several of these compounds.

Following this study, the synthesis of (–)-detoxinine was continued from the equimolar mixture of diastereomers formed with SeO_2, in the hope that a separation might be forthcoming. Fortunately, this turned out to be the case: the diastereomeric Cbz pyrrolidine derivatives **11a**,**b**, formed from **9a**,**b** in 83% yield over two steps, allowed easy separation of the stereoisomers on silica gel (ΔR_f = 0.16), which made possible a stereoconvergent approach to (–)-detoxinine (Scheme 4).



Scheme 4 *Reagents and conditions*: a) $LiAlH_4$, THF, reflux; b) BCN,[11] THF, Et_3N, 20 °C, 83% (2 steps); c) 9-BBN, THF, –20 °C to 20 °C; NaOH, H_2O_2, 84% for **12a**, 85% for **13a**; d) TEMPO, NCS, $NaClO_2$, isoprene, 88% for **12b**, 91% for **13b** (2 steps); e) H_2, $Pd(OH)_2$, MeOH, HCl; f) TFA, CH_2Cl_2, 79% (2 steps); g) CH_2N_2, Et_2O, 92% (ester); h) H_2, $Pd(OH)_2$, EtOAc, AcOH, 40 °C, 82%; i) PCC, CH_2Cl_2; $NaBH_4$, EtOH, 0 °C, 51% (2 steps); j) HCl (3 N), reflux, 85%.

The *cis-syn* isomer **11a**, possessing the required configuration, was first transformed into the natural product. Hydroboration with 9-BBN, followed by oxidation of the intermediate borane, furnish the 1,3-diol **12a** in 84% yield. Other hydroborating agents tested afforded mixtures of the 1,2- and 1,3-diols. Oxidation to the

corresponding acid **12b** proceeded smoothly by using TEMPO, followed by sodium chlorite (88% yield). (–)-Detoxinine was then secured in 79% yield by removal of the Cbz protecting group through catalytic hydrogenation and cleavage of the chiral auxiliary with TFA. The synthetic material {$[\alpha]_D^{20}$ –4.6 (*c* 0.50, H_2O); lit.[3b] $[\alpha]_D^{20}$ –4.4 (*c* 0.50, H_2O), lit.[3d] $[\alpha]_D^{20}$ –4.6 (*c* 0.50, H_2O)}, thus obtained was indistinguishable from an independently prepared sample of (–)-detoxinine (that had been shown to be identical with the naturally derived material).

The *cis-anti* isomer **11b** was next considered. Since neither a Mitsunobu reaction (low yield) nor an oxidation–reduction approach (mostly 1,4-reduction) proved useful for inverting the carbinol center, lactam **14a** was prepared for this purpose. It was reasoned that in the derived ketone the large chiral auxiliary and the folded nature of the bicycle would combine to generate predominantly, if not exclusively, the α-hydroxyl group on hydride reduction. Acid **13b** was thus prepared as was acid **12b** (77% yield) and esterified, and the ester was cyclized to lactam **14a** by carbamate cleavage (75% yield, two steps). As hoped, oxidation of **14a** with PCC, followed by reduction of the resultant ketone with $NaBH_4$, afforded the inverted epimer **14b** as the major product (12:1 ratio), isolated as a single isomer in 51% yield for the two steps. Acid treatment of **14b** then gave in 85% yield (–)-detoxinine, identical with that obtained above.

In summary, (–)-detoxinine has been synthesized in a stereocontrolled approach in 8.3% overall yield starting from (*S*)-1-(2,4,6-triisopropylphenyl)ethanol (**5**). Over the course of this work, an effective preparation of allylic alcohol **9b** has also been realized, which, together with its enantiomer, should allow access to several indolizidine and pyrrolizidine azasugars.

Acknowledgment

We warmly thank Prof. S. E. Denmark for providing a sample of (–)-detoxinine for comparison. We are also grateful to the Research Ministry (MRT grant to J.C.) and the Université Joseph Fourier and the CNRS (UMR 5616, FR2607) for financial support.

References

(1) (a) Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741. (b) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438. (c) Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966. (d) Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383. (e) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660.

(2) For reviews on polyhydroxylated alkaloids, see: (a) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

(3) (a) Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133. (b) Ewing, W. R.; Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Tetrahedron* **1986**, *42*, 2421. (c) Kogen, H.; Kadokawa, H.; Kurabayashi, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1240. (d) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (e) Delle Monache, G.; Misiti, D.; Zappia, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2961. (f) Flögel, O.; Okala Amombo, M. G.; Reissig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, H. *Chem.–Eur. J.* **2003**, *9*, 1405. (g) For (+)-detoxinine: Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1996**, *61*, 566. (h) For a review, see: Li, W.-R.; Han, S.-Y.; Joullié, M. M. *Heterocycles* **1993**, *36*, 359.

(4) For the isolation and biological properties of the detoxin complex, see: (a) Yonehara, H.; Seto, H.; Aizawa, S.; Hidaka, T.; Shimazu, A.; Otake, N. *J. Antibiot.* **1968**, 369. (b) Yonehara, H.; Seto, H.; Shimazu, A.; Aizawa, S.; Hidaka, T.; Kakinuma, K.; Otake, N. *Agric. Biol. Chem.* **1973**, *37*, 2771. (c) Ogita, T.; Seto, H.; Otake, N.; Yonehara, H. *Agric. Biol. Chem.* **1981**, *45*, 2605.

(5) (a) Bateson, J. H.; Quinn, A. M.; Southgate, R. *Tetrahedron Lett.* **1987**, *28*, 1561. (b) Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133.

(6) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6178.

(7) Tamaru, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

(8) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Warpehoski, M. A.; Chabaud, B.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 2897. The allylic oxidation of terminal olefins can be challenging (see ref. 5).

(9) **(4*R*,5*R*)-5-(1-Hydroxyallyl)-4-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one (9a,b).** TBHP (*tert*-butylhydroperoxide, 5 M in decane, 1.8 mL, 9.0 mmol) was added to SeO_2 (254 mg, 2.27 mmol) in 1,2-dichloroethane (10 mL). The mixture was vigorously stirred at 20 °C for 1.5 h and lactam **8b** (1.70 g, 4.58 mmol) in 1,2-dichloroethane (20 mL) was then added rapidly. The resulting mixture was warmed to 70 °C and stirred for 3.3 h. After being allowed to cool to 20 °C, the reaction mixture was treated with an aq solution of $NaHCO_3$ (50 mL), diluted with H_2O (30 mL), and extracted with EtOAc (3 × 120 mL). The combined organic extracts were washed with aq Na_2SO_3 (120 mL), H_2O (120 mL), and brine (120 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil in 7 mL of EtOH at 0 °C was treated with 171 mg (0.46 mmol) of $CeCl_3 \cdot 7H_2O$, followed by 17.3 mg (0.46 mmol) of $NaBH_4$ (to reduce the 5–10% of enone). After 1 h, the reaction mixture was processed with EtOAc in the usual way and the crude product was purified by flash chromatography on silica gel with EtOAc in CH_2Cl_2 (40–100%) to afford 440 mg of recovered **8b**, followed by 988 mg (56%; 75% based on recovered starting material) of **9a**,**b** as a white solid. Extensive purification of this material over silica gel provided enriched samples of **9a** and **9b** for spectral data.
Compound **9a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (s, 1 H), 6.99 (s, 1 H), 5.80 (ddd, *J* = 17.3, 10.7, 4.4 Hz, 1 H), 5.42 (dt, *J* = 17.3, 1.7 Hz, 1 H), 5.27 (dt, *J* = 10.7, 1.7 Hz, 1 H), 5.18 (q, *J* = 6.9 Hz, 1 H), 4.61 (m, 1 H), 4.35 (q, *J* = 7.5 Hz, 1 H), 3.82 (sept, *J* = 6.7 Hz, 1 H), 3.65 (dd, *J* = 7.6, 1.4, 1 H), 3.16 (sept, *J* = 6.7 Hz, 1 H), 2.87 (sept, *J* = 6.9 Hz, 1 H), 2.61 (dd, *J* = 16.7, 6.7 Hz, 1 H), 2.54 (dd, *J* = 16.6, 7.9 Hz, 1 H), 1.61 (d, *J* = 6.8 Hz, 3 H), 1.31–1.18 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4, 149.0, 148.5, 146.8, 136.7, 123.8, 121.3, 117.0, 72.7, 72.1, 70.8, 60.9, 37.7, 34.4, 29.6, 28.6, 25.6, 25.5, 25.4, 24.6, 24.3, 23.6.
Compound **9b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (s, 1

H), 7.00 (s, 1 H), 5.86 (ddd, *J* = 17.3, 10.5, 6.8 Hz, 1 H), 5.39 (dt, *J* = 17.3, 1.2 Hz, 1 H), 5.32 (dt, *J* = 10.4, 1.1 Hz, 1 H), 5.20 (q, *J* = 6.7 Hz, 1 H), 4.45–4.35 (m, 2 H), 3.72 (sept, *J* = 6.9 Hz, 1 H), 3.56 (td, *J* = 7.7, 1.1 Hz, 1 H), 3.38 (d, *J* = 2.3 Hz, 1 H), 3.17 (sept, *J* = 6.8 Hz, 1 H), 2.88 (sept, *J* = 6.9 Hz, 1 H), 2.56 (d, *J* = 8.0 Hz, 1 H), 1.63 (d, *J* = 6.8 Hz, 3 H), 1.34–1.18 (m, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 149.1, 148.7, 146.6, 137.0, 123.8, 121.4, 118.9, 73.6, 73.0, 60.3, 36.6, 34.4, 29.6, 29.0, 25.6, 25.5, 25.3, 24.5, 24.3, 23.5.

(10) The relative stereochemistry in **9a** and **9b** was assigned from the NMR of derivatives prepared in a concomitant project (to be published); these assignments were confirmed by the successful synthesis of (–)-detoxinine.

(11) Henklein, P.; Heyne, H.-U.; Halatsch, W.-R.; Niedrich, H. *Synthesis* **1987**, 166.