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A Synthetic Approach towards Octalactin A, Based on the Stereoselective Reduction of α,β-Unsaturated Ketones

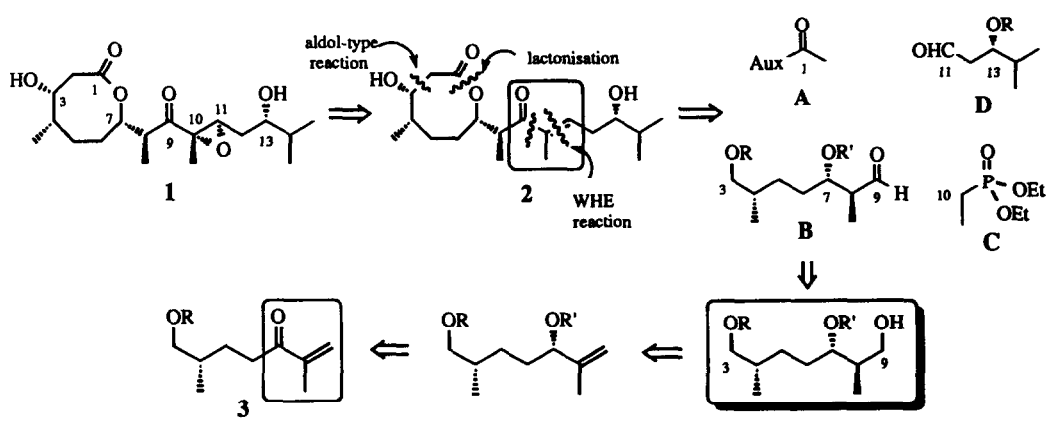
Jordi Bach, Ramon Berenguer, Jordi Garcia,* and Jaume Vilarrasa

Departament de Química Orgànica, Div. III, Universitat de Barcelona
c/ Martí i Franquès 1-11, 08028 Barcelona, Catalonia, Spain

Abstract: An efficient enantioselective synthesis of the C3–C9 fragment of Octalactin A and studies aimed at the conversion of Octalactin B into Octalactin A are described, which are based on the borane-mediated reduction of α,β-unsaturated ketones catalysed by *B*-methyl-4,5,5-triphenyl-1,3,2-oxaza-borolidines (**9**). A comparative study of the reduction of 2-methylnon-1-en-3-one (**10**) —a model of the Octalactin-A C3–C9 moiety— with different chiral reagents has also been performed.

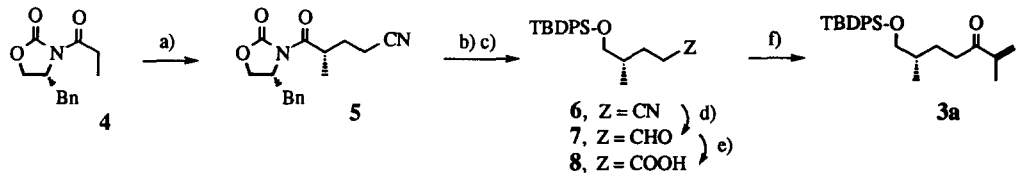
In 1991, Fenical, Clardy *et al.* reported[1] the isolation and relative configuration of Octalactin A (**1**) and Octalactin B (**2**), two closely related metabolites isolated from marine-derived fungi of the genus *Streptomyces*. Both compounds contain an eight-membered lactone ring. This unusual structural feature and the strong cytotoxicity displayed by **1** against some tumor cell lines make these compounds very attractive as synthetic targets.

In 1994, Buszeck *et al.*[2] elucidated the absolute configuration of **1** and **2** by total synthesis starting from methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionates. Shortly afterwards, Clardy *et al.* reported[3] the synthesis of (+)-**1** and (+)-**2**, the enantiomers of the naturally ocurring Octalactins, from (+)-citronellic acid. These reports have prompted us to disclose here our approach to the enantioselective total synthesis of **1**, which is based on a completely different strategy: in our retrosynthetic analysis, summarised in Scheme 1, **1** arises from **2** which, in turn, can be disconnected into fragments or synthons **A**, **B**, **C**, and **D**; the key steps, as far as the control of stereoselectivity is concerned, are the reduction of the CO group of α,β-unsaturated ketone **3** as well as that of the lateral chain of **2** (followed by a diastereoselective epoxidation and re-oxidation of the C9-OH).



Scheme 1

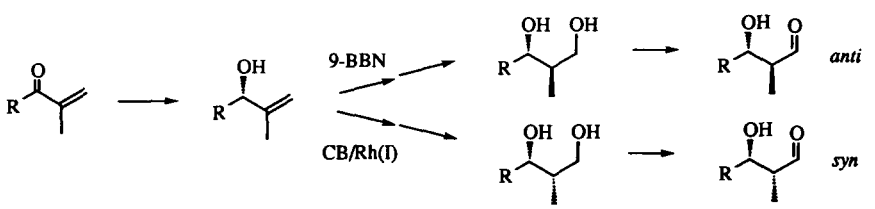
Compound **3a** (**3**, with R = Bu^{t}Ph$_2$Si = TBDPS) was obtained in 52% overall yield as shown in Scheme 2. Michael addition of the titanium enolate derived from Evans' *N*-acyloxazolidinone **4** to acrylonitrile was readily carried out at a 15 g bench scale.[4] After reductive removal of the chiral auxiliary[5] from **5** and *in situ* protection of the primary alcohol, the nitrile group was cleanly converted into aldehyde **7** by DIBALH reduction. Oxidation with $NaClO_2/H_2O_2$,[6] in turn, afforded carboxylic acid **8**. Transformation of **8** into **3a** was successfully achieved by sequential addition of 1 equiv. of BuLi and 1 equiv. of CH_2=C(CH$_3$)Li.[7]



Scheme 2. a) $TiCl_3(O^iPr)$, DIPEA, CH_2Cl_2, 0°C, then acrylonitrile (90%, 97.4% d.e.); b) $LiBH_4$, MeOH, THF, 0 °C; c) TBDPSCl, Py, r.t. (75% overall **5**-**6**); d) DIBALH, Et_2O, –78 °C (93%); e) $NaClO_2$, H_2O_2, aq. NaH_2PO_4, r.t. (95%); f) (from **8**) BuLi, THF, 0 °C, then CH_2=C(CH$_3$)Li (88%).

Asymmetric reduction of α,β-unsaturated ketones

As suggested in Scheme 1, asymmetric reduction of enone **3** seemed us an interesting approach to fragment **B**, since the corresponding allylic alcohol could potentially be transformed *via* hydroboration, followed by selective oxidation of the primary hydroxy group, into either *anti*-aldols or *syn*-aldols depending upon the reaction conditions used (9-BBN or catecholborane/Wilkinson's catalyst, see Scheme 3).[8]



Scheme 3

Very recently, we have reported on (*R*)- and (*S*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine **9**, two new catalysts derived from inexpensive phenylglycine, which we have utilised in the borane-mediated reduction of prochiral ketones.[9] When (*R*)-**9** was applied to the reduction of 2-methylnon-1-en-3-one (**10**), which was chosen as a model of **3**, a clean conversion to allylic alcohol **11** was observed (98% yield, 92% e.e.). Table 1 shows a comparative study performed with a few representative reducing agents;[10] it is noteworthy that none of them improved the results arising from (*R*)-**9**.

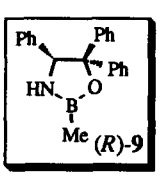
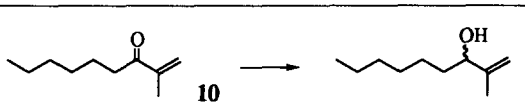
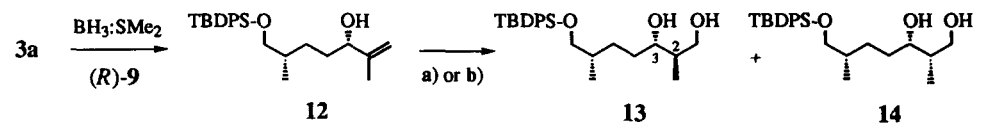


Table 1. Enantioselectivity in the reduction of 10 with different reagents



i)	BH_3, cat. (*R*)-**9**, THF, 0 °C	92% e.e. (*S*)	iv)	$LiAlH_4$, (–)-*N*-methylephedrine,[10c] *N*-ethylaniline, –78 °C	84% e.e. (*R*)
ii)	BH_3, CBS cat.,[10a] THF, 0 °C	92% e.e. (*R*)	v)	$LiAlH_4$, (–)-*N*-methylephedrine,[10c] 2-(ethylamino)pyridine, –78 °C	54% e.e. (*S*)
iii)	$LiAlH_4$, (+)-1,1'-bis(2-naphthol),[10b] EtOH, THF, –100 °C to –78 °C	89% e.e. (*R*)	vi)	$LiBH_4$, THF, Bu^{t}OH *N,N'*-dibenzoyl-L-cystine,[10d] –78 °C	35% e.e. (*R*)

In the light of these results, we treated **3a** with borane in the presence of (*R*)-**9**, which gave allylic alcohol **12** in 95% yield and 91% d.e.[11] As expected,[8a] hydroboration of **12** with an excess of 9-BBN in THF followed by oxidation led mainly to **13** (2,3-*anti*), corresponding to the C3-C9 fragment of Octalactin A. An attempt aimed at achieving the one-pot transformation of **3a** into **13** (reduction with borane and (*R*)-**9**, followed by treatment with 9-BBN and oxidation) gave a lower selectivity (92%, *anti*/*syn* 4.5:1). On the other hand, hydroboration with CB/Rh(I) gave predominantly the *syn* isomer (93%, *anti*/*syn* 1:3).



a) 1) 9-BBN; 2) H_2O_2, $NaHCO_3$ 90%; **13/14** = 9:1
b) 1) Bu^{t}COCl, Py; 2) 9-BBN, THF 62%; **13/14** = 15:1
3) H_2O_2, $NaHCO_3$; 4) $LiAlH_4$

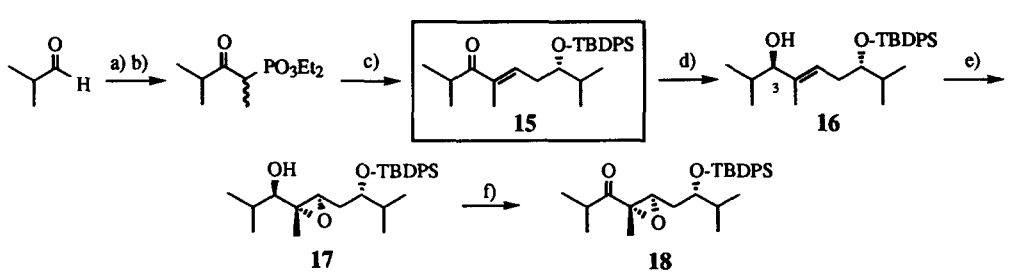
Scheme 4

An improvement in selectivity was obtained when the 3-*O*-pivaloyl derivative of **12** was treated with 9-BBN in THF (sequence **b**, Scheme 4).[12] After deprotection of the secondary hydroxy group, a gratifying 15.4:1 diastereomeric ratio was achieved.[13]

From Octalactin B to Octalactin A

We have also explored the potential application of oxazaborolidines **9** with regard to the transformation of protected Octalactin B into Octalactin A. Provided that the stereoselective reduction of the carbonyl group of Octalactin B could be accomplished, the C9-OH-directed epoxidation[14] followed by re-oxidation to the ketone would lead to protected Octalactin A.

Enone **15**, a model of Octalactin B, was obtained as a single stereoisomer *via* a Horner–Wadsworth-Emmons reaction promoted by active $Ba(OH)_2$[15] from the corresponding phosphonate and protected (*S*)-3-hydroxy-4-methylpentanal[16] (see **D** in Scheme 1). Reduction of **15** with borane and (*R*)-**9** cleanly afforded allylic alcohol **16** (7:1 diastereomeric ratio),[11] which was converted into epoxy ketone **17** (see Scheme 5). As expected, reduction of **15** using (*S*)-**9** yielded the epimer at C3 of **16** (1:7 diastereomeric ratio). It is worth noting that catalyst (*R*)-**9** leads to products of opposite configuration at the new stereocenter of **12** and **16**.



Scheme 5. a) $EtPO_3Et_2$, Bu^{t}Li, THF, –78 °C (90%); b) Swern oxidn. (95%); c) (*S*)-3-hydroxy-4-methylpentanal TBDPS ether, $Ba(OH)_2$-$8H_2O$, wet THF (93%); d) BH_3:SMe_2, (*R*)-**9** (1 equiv.), THF, 0 °C (94%); e) Bu^{t}OOH, $VO(acac)_2$ cat., benzene, r.t. (80%); f) Swern oxidn. (90%).

In summary, catalyst (*R*)-**9** has been applied to an Octalactin A synthesis in two respects: (i) an efficient synthesis of C3-C9 fragment and (ii) a stereoselective synthesis of compound **18**, a model of the C9-C15 fragment. The total synthesis of the Octalactins will be reported in full in due course.

Acknowledgements

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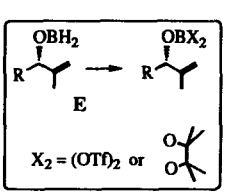
1. Tapiolas, D.M.; Roman, M.; Fenical, W.; Stout, T.J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682.
2. Buszek, K.R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511.
3. McWilliams, J.C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378.
4. Evans, D.A.; Bilodeau, M.T.; Somers, T.C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750.
5. Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
6. Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
7. Alternatively, **3a** was also obtained by addition of CH_2=C(CH_3)MgBr to aldehyde **7**, followed by oxidation with MnO_2. Several attempts of direct transformation of **6** into **3a** by addition of organolithium or Grignard reagents failed.
8. (a) Still, W.C.; Barrish, J.C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (b) Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (c) For a recent review on catalysed hydroborations, see: Burgess, K; Ohlmeyer, M.J. *Chem. Rev.* **1991**, *91*, 1179.
9. Berenguer, R.; Garcia, J.; Gonzàlez, M.; Vilarrasa, J. *Tetrahedron:Asymmetry* **1993**, *4*, 13; Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron:Asymmetry* **1994**, *5*, 165.
10. a) CBS reagent: (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole (Corey, E.J.; Shibata, S.; Bakshi, R.K. *J. Org. Chem.* **1988**, *53*, 2861 and ref. therein); in a similar reduction carried out at low temperature with catecholborane instead of borane, lower yield and selectivity were observed (58%, 86% e.e.); b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717; c) Terashima, S.; Tanno, N.; Koga, K. *J.C.S. Chem. Comm.* **1980**, 1026; Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* **1984**, 239; d) Soai, K.; Oyamada, H.; Yamanoi, T. *J.C.S. Chem. Comm.* **1984**, 413.
11. D.e. of the alcohol was determined by HPLC analysis of the Mosher ester. The absolute configuration was established by the Kakisawa method (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092) and confirmed by comparison of the allylic alcohol derived from Sharpless' epoxidation of a mixture of epimers.
12. It is known (ref. 8c) that electron-withdrawing and/or sterically demanding groups on the allylic oxygen favour diastereoselectivity in the hydroboration. In fact, attempts at searching for a more selective process (by using an *in situ* conversion of OBH_2 —see transient intermediate **E**— to a more electron-withdrawing and/or bulkier OBX_2 group, before hydroboration) were unsuccessful.



13. Compounds **13** and **14** could be separated by column chromatography. The mixtures were analysed by HPLC of the Mosher diester. The relative configurations of both compounds were determined by NMR analysis of the *p*-methoxybenzylidene acetal derivatives.
14. A similar directed epoxidation is reported in Buszek's approach (ref. 2). However, in this case the hydroxylic substrate was not obtained in a stereoselective manner, but rather as a mixture of epimers differing in configuration at C9. By contrast, in the Clardy synthesis (ref. 3), the introduction of the epoxide group has been reported to occur in a 2:1 diastereomeric ratio by nucleophilic epoxidation on (+)-Octalactin B.
15. Paterson, I.; Yeung, K.; Smaill, J.B. *Synlett* **1993**, 774. Other bases (*e.g.* LiCl/DBU or NaH) gave poorer results.
16. Protected (*S*)-3-hydroxy-4-methylpentanal was synthesised by ozonolysis of *O*-silylated (*S*)-2-methylhex-5-en-3-ol (95% e.e.) obtained by asymmetric allylboration of isobutyraldehyde (Racherla, U.S.; Brown, H.C. *J. Org. Chem.* **1991**, *56*, 401).

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