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Stereoselective reduction of α'-branched α,β-ynones. Application to the synthesis of the Octalactin A ring

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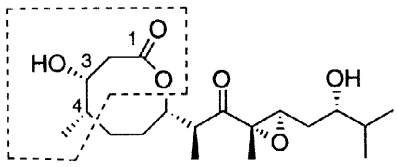
Abstract

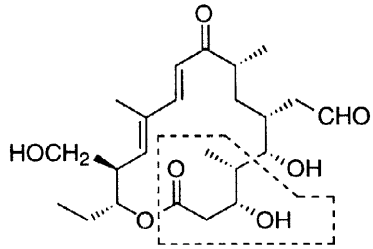
A flexible, efficient route to chiral 3-hydroxy-4-methyl- and 3-hydroxy-4-methoxyalkanoic acids, with high control of the C(3) configuration, has been disclosed, which is based on the borane-mediated reduction of 1-trimethylsilyl-1-alkyn-3-ones (**6**) in the presence of oxazaborolidine **7** followed by hydroboration of the resulting propargylic alcohols **4** and **5**. This strategy has been applied to the synthesis of the Octalactin A ring.

Keywords: Diastereoselection; Marine metabolites; Oxazaborolidines; Reduction

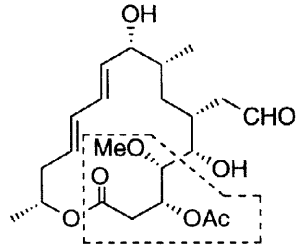
Octalactin A (**1**) is a metabolite, recently isolated from a marine actinomycete [1], which shows a potent cytotoxicity against some human tumor cell lines. The unusual structural feature and biological activity of **1** have stimulated a few groups [2–5] to undertake its synthesis. In this connection, we have now addressed ourselves to the construction of the C(1)-C(4) fragment, namely a 3-hydroxy-4-methylbutanoic acid moiety embedded in a eight-membered lactone ring. Similar, relatively simple chiral synthons (or their 4-methoxy



1
Octalactin A



Tylonolide



Leucomycin aglycone

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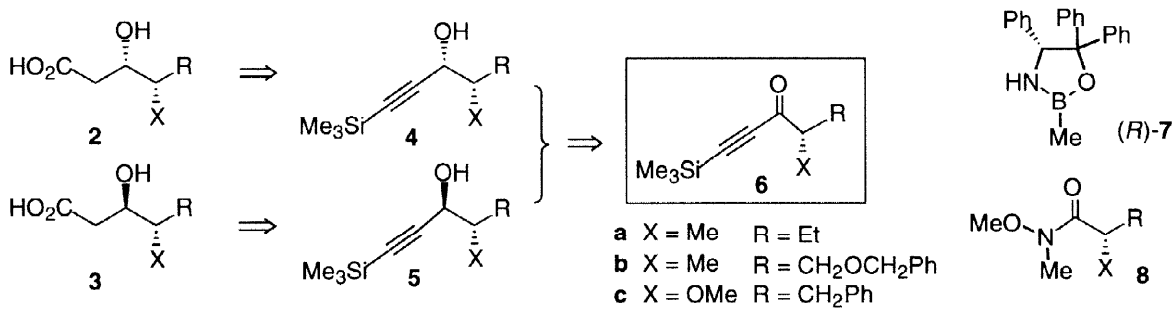
analogues) are common structural elements of other biologically active natural and synthetic macrolides of interest in pharmacy and veterinary (*e.g.* tylosin and leucomycins) [6]. Obvious ways of building up such substructures (like **2** and **3**) include allylboration [7] and acetate aldol reaction [8] of the appropiate chiral α-substituted aldehydes, but the stereochemical control at the emergent stereocenter C(3) is not always satisfactory (specially in the mismatched case). Taking advantage of our previous experience in the reduction of acetylenic ketones [9], we report herein an alternative, efficient route to compounds **2** and **3** (or their enantiomers), via alcohols **4** and **5**, based on the reduction of chiral ketones **6** with BH_3:SMe_2 in the presence of oxazaborolidines (*R*)- or (*S*)-**7**, followed by hydroboration (Scheme 1). We have also successfully applied this strategy to the construction of the Octalactin A ring.

Scheme 1



We prepared a set of representative ynones **6a–c** by addition of $Me_3SiC{\equiv}CLi$ (2 equiv.) to the Weinreb amides **8a–c** (86–90% yield, THF, 0 °C)[1] which, in turn, were readily obtained by standard methods from the corresponding chiral acids or methyl esters [10]. Reductions of **6**

Table 1
Reduction of ketones 6 with BH_3:SMe_2 in the presence of 7 in THF at 0 °C

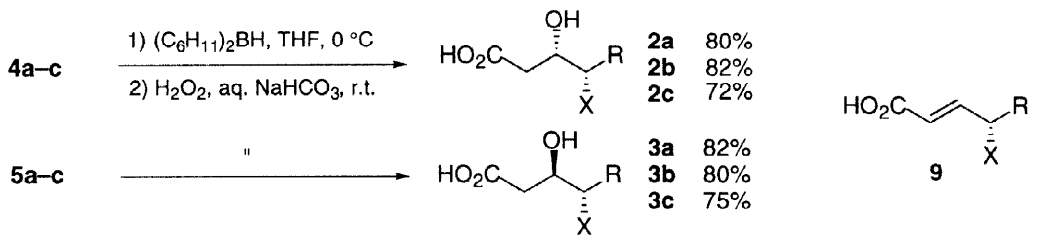
ketone	catalyst	yield[a]	ratio **4** : **5**[a,b]
6a	(*R*)-**7**	97% (90%)	96 (95) : 4 (5)
6a	(*S*)-**7**	90% (91%)	4 (5) : 96 (95)
6b	(*R*)-**7**	75% (70%)	98 (96) : 2 (4)
6b	(*S*)-**7**	80% (71%)	2 (6) : 98 (94)
6c	(*R*)-**7**	74% (70%)	97 (88) : 3 (12)
6c	(*S*)-**7**	80%	9 : 91

[a]Values are referred to 1 equiv. of oxazaborolidine **7**. Within parentheses, values using 0.2 equiv. of **7**.
[b]Determined by ^{19}F NMR analysis of the corresponding Mosher esters. Configuration at C(3) was determined by the Kakisawa method [11]. In addition, stereochemistry of **5a** was confirmed by chemical correlation, through **3a**, with the known methyl ester of (3*R*,4*S*)-3-hydroxy-4-methylhexanoic acid [12].

[1]Besides ketones **6**, a small amount (5–8%) of desilylated ketones were also isolated by flash chromatography.

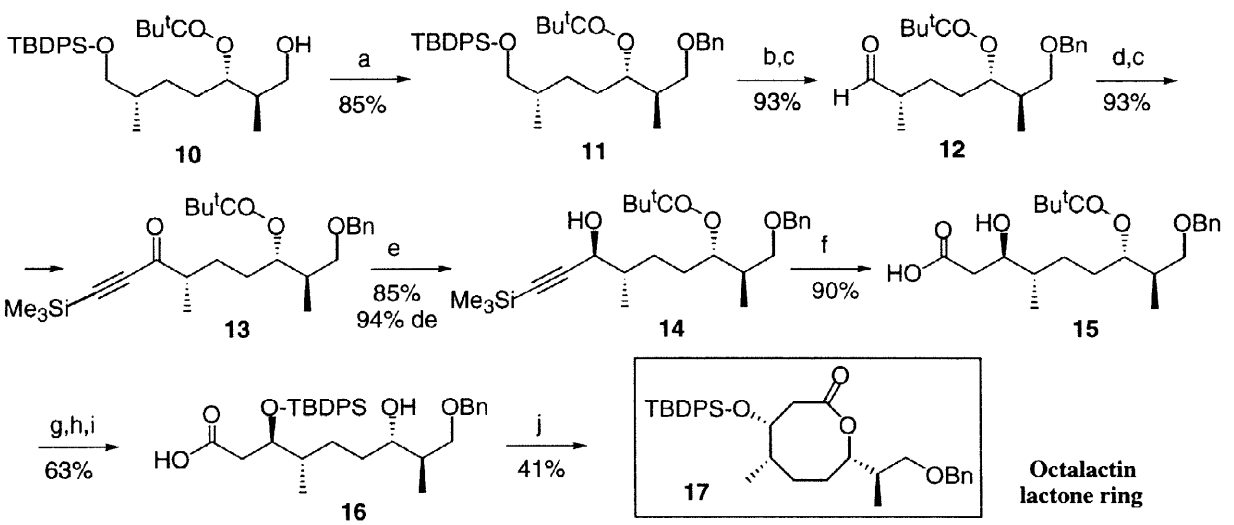
were performed by slow addition (~30 min) of the ketone (1 mmol) to a solution of BH_3:SMe_2 (1 mmol) in THF (2 mL) with 0.2–1.0 mmol of (*R*)- or (*S*)-**7** under Ar at 0 °C. The results are summarized in Table 1. As expected, the stereoselectivity derived from the oxazaborolidine **7** overcame the intrinsic facial bias of the carbonyl group of ketones **6** resulting in good to excellent diastereoselectivities even in the mismatched cases. Hydroboration of **4** and **5** with $(C_6H_{11})_2BH$ [13] followed by oxidation of the alkenylborane resulted in isolation of β-hydroxy acids **2** and **3**, respectively, in good yield (Scheme 2).[2]

Scheme 2



These remarkable results prompted us to apply this strategy to an Octalactin ring synthesis (Scheme 3). Accordingly, advanced intermediate **10** [4] was transformed into aldehyde **12** by standard methods. Addition of lithium trimethylsilylacetylide to **12** provided a roughly equimolar, inseparable mixture of ynols (**14** and its epimer). Swern oxidation of such a mixture yielded acetylenic ketone **13**. To our satisfaction, the borane-mediated reduction of **13**

Scheme 3



a) CCl_3C=NH(OBn), $TfOSiMe_3$ cat. b) TBAF, THF, r.t. c) Swern oxidn. d) TMSC≡CLi, THF, –78 °C. e) BH_3: SMe_2, (*S*)-**7** (1 equiv.), THF, 0 °C. f) *i*) $(C_6H_{11})_2BH$, THF, r.t.; *ii*) H_2O_2, aq. $NaHCO_3$; *iii*) AcOH. g) TBDPSCl, imidazole, DMF. h) aq. $NaHCO_3$, r.t., then AcOH. i) DIBALH (3 equiv.), CH_2Cl_2, –78 °C. j) $(PyS)_2$, PPh_3; $AgBF_4$, toluene, Δ.

[2]It is noteworthy that the use of aq. $NaHCO_3$ (or aq. NaOH if compatible with other funcionalities on the substrate) is crucial in the oxidation step. Neutral media (phosphate buffer) led mainly to **9** (probably by elimination of borate or boronate moieties). On the other hand, when the OH group was protected as silyl ether or pivaloate ester **9a–c** were the only isolated products [14].

in the presence of (*S*)-**7** (1 equiv.) gave **14** in 85% yield and 94% d.e. As expected, hydroboration of **14** with an excess of $(C_6H_{11})_2BH$ in THF, followed by treatment with H_2O_2 and aq. $NaHCO_3$ afforded β-hydroxy acid **15** in excellent yield. Transformation of **15** into the *seco*-acid **16** required three additional steps. Protection of hydroxyl at C(3) led to concomitant formation of silyl ester which had to be further hydrolysed with aq. $NaHCO_3$. Subsequent deprotection of the pivaloyl group was troublesome. Initial attempts employing nucleophiles such as hydrazine or Grignard reagents failed on such a hindered ester. Cleavage was accomplished, without affecting the carboxyl group nor *t*-butyldiphenylsilyl protecting group, using DIBALH in CH_2Cl_2 at –78 °C. Finally, the ring closure was carried out by the Corey-Gerlach procedure [15,16] under high-dilution conditions [17].[3]

In summary, we have demonstrated that the tandem stereoselective reduction/ hydroboration applied to chiral trimethylsilyl acetylenic ketones affords 3-hydroxy-4-methyl- and 3-hydroxy-4-methoxyalkanoic acid synthons with high control on C(3) configuration. This strategy has been applied to the synthesis of the Octalactin A ring.

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[3] **Compound 17.** ^1H NMR ($CDCl_3$, 500 MHz, *J* in Hz): δ 0.95 (d, 3H, *J*=7.0), 0.96 (d, 3H, *J*=4.5), 1.09 (s, 9H), 1.20–1.80 (m, 5H), 1.96 (m, 1H), 2.50 (dd, 1H, *J* =12.5, 2.5), 2.68 (dd, 1H, *J* =12.5, 7.0), 3.37 (dd, 1H, *J* =9.0, 4.5), 3.50 (dd, 1H, *J*=9.0, 5.0), 3.95 (m, 1H), 4.31 (m, 1H), 4.41 (s, 2H), 7.20-7.40 (m, 15H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 13.9, 19.5, 24.3, 27.0, 29.7, 31.1, 38.5, 38.6, 39.4, 71.8, 73.2, 73.8, 78.3, 127.4, 127.5, 127.6, 128.3, 129.6, 129.7, 133.8, 134.8, 135.3, 136.2, 136.5, 138.5, 172.1. IR (film) ν: 1732 cm^{-1}. HRFABMS calcd. for $C_{34}H_{44}NaO_4Si$ (M+Na) m/z 567.2917, found 567.2907.