Tetrahedron Letters 53 (2012) 3250–3253

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient total synthesis of manzacidin B

Tetsuro Shinada *, Kentaro Oe, Yasufumi Ohfune *

Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

ARTICLE INFO

Article history:
Received 9 March 2012
Revised 3 April 2012
Accepted 9 April 2012
Available online 20 April 2012

Keywords:
Manzacidin B
[Bis(*N*-*tert*-butylsalicyliden-iminate)]copper catalyst
Isocyanoacetate aldol reaction
Oppolzer's camphorsultam

ABSTRACT

The highly diastereoselective synthesis of the marine natural product, (−)-manzacidin B, is described. A novel copper-catalyzed aldol reaction of the α-methylserine-derived aldehyde with an isocyanoacetate possessing (1*R*)-camphorsultam as the chiral auxiliary proceeded in a highly diastereoselective manner to give the (4*R*,5*R*,6*R*)-adduct, which was converted into manzacidin B in a few steps.

Bromopyrrole alkaloids are a novel family of marine natural products possessing potentially useful pharmacological activities which include α-adrenoceptor blockers, antagonists of serotonergic receptors, and actomyosin ATPase activators.[1] Among them, manzacidins A (**1**), B (**2**), and C (**3**), isolated from the Okinawan sponge *Hymeniacidon* sp. in 1991 by Kobayashi et al., possess a unique structure consisting of an ester-linked bromopyrrolecarboxylic acid and a 3,4,5,6-tetrahydropyrimidine ring in which one of the amino groups is attached to the C6 quaternary carbon center.[2,3] Due to their unique structures and detailed unexploited pharmacological profiles, the manzacidins have been intriguing synthetic target molecules.[4] The relative and absolute structures of **1** and **3** have been confirmed by our first total syntheses.[5a] The relative structure of manzacidin B (**2**), reported by Kobayashi et al.,[2] was determined by the synthesis of four possible diastereomers with respect to the C4 and C5 stereogenic centers.[6a] Finally, the structure was unambiguously assigned (4*R*,5*R*,6*R*)-**2** by the X-ray crystallographic analysis of its synthetic intermediate (4*R*,5*R*,6*R*)-**4** (vide infra) (Fig. 1).[6b] The synthesis of **2** including its enantiomer and diastereomer has, recently, been reported by Mohapatra et al.[4i]

In our previous studies, we performed the synthesis of manzacidin B using the Cu-catalyzed Ito–Hayashi type aldol reaction[7] of the α-methyl-Garner aldehyde **5a** with *t*-butyl isocyanoacetate as the key step (Scheme 1). The reaction gave a mixture of *trans*-oxazolines (4*R*,5*R*,6*R*)-**6** and (4*S*,5*S*,6*R*)-**7** (future manzacidin numbering) in 88% yield. Although the desired adduct **6** corresponding to the natural **2** was obtained as the minor isomer (**6**/**7** = 1:7),[6a,8] the inversion of the stereoselectivity from (4*S*,5*S*)-**7** to (4*R*,5*R*)-**6** would provide an efficient synthetic route to manzacidin B. In this letter, we describe the short and highly stereoselective synthesis of **2** by the Cu-catalyzed aldol reaction using an isocyanoacetate possessing a chiral auxiliary.

To achieve the requisite (4*R*,5*R*)-selectivity in the isocyanoacetate aldol reaction, reagent-controlled approaches (screening of bases and catalysts), substrate-controlled approaches (the use of structurally alternate aldehydes of **5a**), and a double asymmetric induction[9] using a chiral aldol donor were extensively examined (Scheme 1).

The catalyst screening was carried out according to the previous reaction conditions[6a] using 5 mol % Et_3N as the base, since other organic bases, such as *i*-Pr_2NH, *i*-Pr_2NEt, DBU, and DABCO, did not affect the reaction in terms of the reaction rate, diastereoselec-

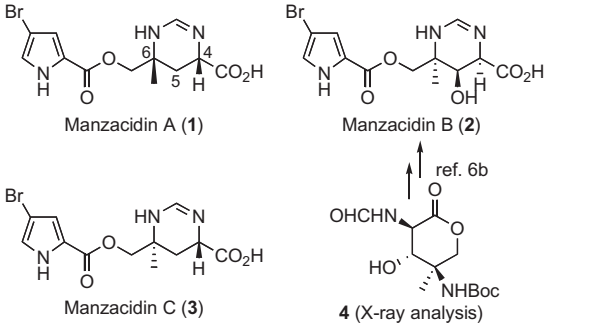
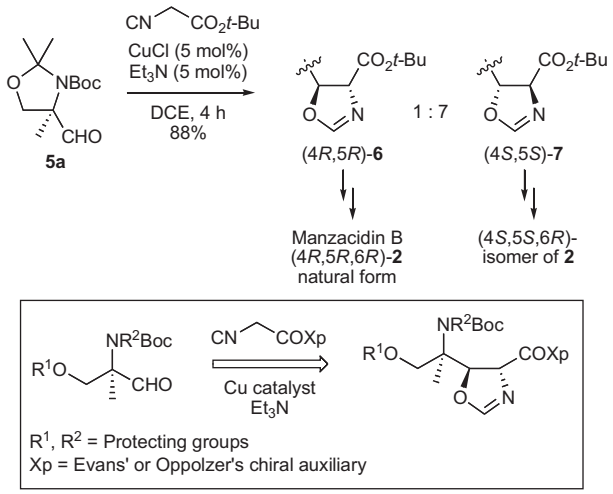


Figure 1. Structures of the manzacidins.

* Corresponding authors. Tel.: +81 6 6605 2570; fax: +81 6 6605 3153 (Y.Ohfune).
E-mail addresses: shinada@sci.osaka-cu.ac.jp (T. Shinada), ohfune@sci.osaka-cu.ac.jp (Y. Ohfune).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.04.042



Scheme 1. Previous results and present synthetic plan.

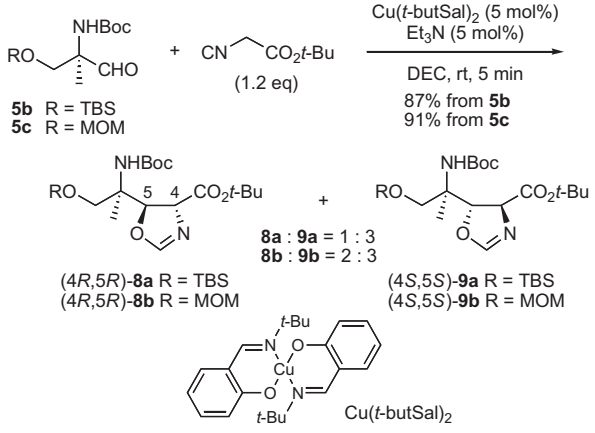
tivity, and yields. Among the screening of several metal catalysts, Cu(I) significantly accelerated the reaction rate and increased its yield. In particular, the [bis(*N*-*tert*-butylsalicyliden-iminate)]copper (Cu(*t*-butSal)$_2$) catalyst dramatically enhanced the reaction rate and its yield (5 min, 94%) in comparison to CuCl (4 h, 88%). However, the diastereomeric ratio of the products, (4*R*,5*R*)-**6**/(4*S*,5*S*)-**7**, was not affected by this and other catalysts.[10] We considered that the above propensities would be due to the rigid and densely functionalized structure of the aldehyde **5a** which facilitated the substrate-controlled aldol reaction. Therefore, we turned our attention to the use of the ring-opened aldol acceptors **5b**,**c**,[11] readily prepared from α-methylserine.[12]

The treatment of **5b**,**c** under the same reaction conditions gave a mixture of the *trans*-oxazolines, in which the undesired (4*S*,5*S*)-selectivity was decreased, that is (4*R*,5*R*)-**8a**/(4*S*,5*S*)-**9a** = 1:3 and (4*R*,5*R*)-**8b**/(4*S*,5*S*)-**9b** = 2:3 (Scheme 2).[5b,13] These results indicated that the released ring constraint of the aldol acceptors was moderately associated with the diastereoselectivity (**6**:**7** = 1:7 vs **8**:**9** = 1–2:3).

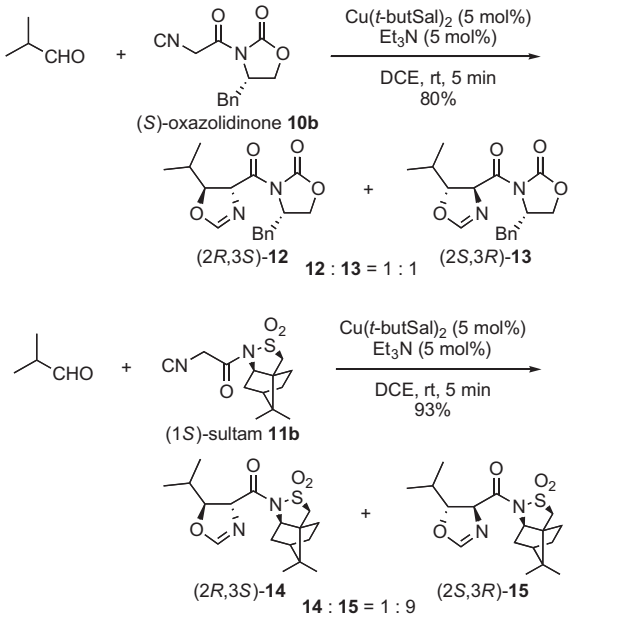
These results as mentioned above led us to speculate that the combination of the ring-opened aldehyde **5b,c** with an isocyanoacetate possessing a chiral auxiliary would inverse the undesired (4*S*,5*S*)-selectivity to the desired (4*R*,5*R*)-isomer by the double asymmetric induction, while the aldol reaction using a chiral isocyanoacetate has not yet been reported. We chose both enantiomers of the isocyanoacetate bearing Evans' oxazolidinone, (*R*)-**10a,** and (*S*)-**10b**,[14] and Oppolzer's camphorsultam, (1*R*)-**11a,** and (1*S*)-**11b**.[11,15] To investigate the unprecedented reactivity and diastereoselectivity of the chiral isocyanoacetate aldol reaction, we performed the reactions of **10b** and **11b** with achiral isobutyraldehyde. These reactions were catalyzed by Cu(*t*-butSal)$_2$ to give a mixture of the aldol products in excellent yields. The use of the (1*S*)-camphorsultam **11b** showed a significant (2*S*,3*R*)-selectivity ((2*R*,3*S*)-**14**/(2*S*,3*R*)-**15** = 1:9), while the (*S*)-oxazolidinone **10b** afforded a 1:1 mixture of the *trans*-oxazolines, **12,** and **13** (*cis*/*trans* = 1/13).[16–18] Thus, the chiral camphorsultam **11** was found to be a superior chiral auxiliary to the oxazolidinone **10** in view of the single asymmertric induction (Scheme 3).

With these results in hand, we attempted the double asymmetric induction using the chiral aldehydes **5b,c** with each enantiomer of the chiral aldol donors, **10a**,**b,** and **11a**,**b**. Both Evans-type aldol donors, **10a**,**b** were ineffective for the (4*R*,5*R*)-selectivity in all cases to give a mixture of the corresponding aldol adducts, ((4*R*,5*R*)-isomer/(4*S*,5*S*)-isomer = 1–2:3),[19] as observed during the aldol reaction of **5b,c** with the achiral *tert*-butyl isocyanoacetate (1–2:3). On the other hand, the use of camphorsultams, **11a**,**b** exhibited remarkable diastereoselectivities for the aldol reaction. To our delight, the reaction of the ring-opened aldehyde **5b** with (1*R*)-**11a** showed the (4*R*,5*R*)-selectivity for the first time to give the desired (4*R*,5*R*)-**16a** as the major isomer (59%, **16a**/**17a** = 13:1). The use of the MOM-protected **5c** with (1*R*)-**11a** was the best combination to obtain (4*R*,5*R*)-**16b**[20] in view of the yield and diastereoselectivity (84%, dr = 13:1). The reaction of **5b,c** with (1*S*)-**11b**, the enantiomer of **11a**, afforded (4*S*,5*S*)-**19a,b** as an exclusive diastereomer, respectively (Scheme 4).[21] The exclusive formation of (4*S*,5*S*)-**19a,b** (>20:1) from the aldehydes **5b,c** with (1*S*)-**11b** can be explained as a matched pair double asymmetric induction.[9] On the other hand, in spite of the mismatched pair between **5b,c** and (1*R*)-camphorsultam **11a** , the chiral auxiliary-based diastereocontrol would be attributed to the high diastereoselective formation of the desired (4*R*,5*R*)-**16a,b** (13:1).

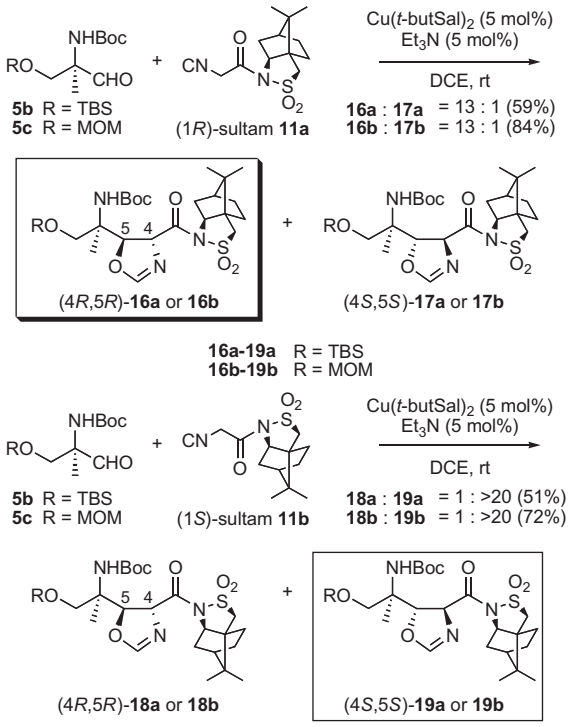
A proposed transition state model of the chiral camphorsultam aldol reaction to give **16b** is depicted in Scheme 5. To avoid steric and/or electronic repulsions between the isocyanide and sulfone groups, the *Z*-enolate would be preferentially formed.[15,16] In this



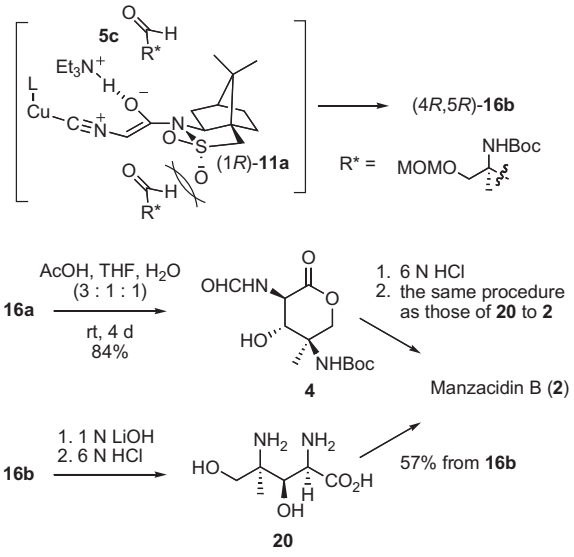
Scheme 2. Cu(*t*-butSal)$_2$-catalyzed aldol reaction of **5b**,**c**.



Scheme 3. Chiral auxiliary-assisted isocyanoacetate aldol reactions with isobutyraldehyde.



Scheme 4. Aldol reactions of ring-opened aldehydes **5b**,**c** with isocyanoacetate bearing the chiral camphorsultam.



Scheme 5. Proposed transition state model and conversion to manzacidin B.

model, approaches from the *re*-face of the *Z*-enolate of (1*R*)-**11a** and the *re*-face of the aldehyde **5c** would be the kinetically favored process to give (4*R*,5*R*)-**16b** as the major diastereomer. The structure of **16a** was unambiguously assigned to the (4*R*,5*R*,6*R*)-isomer by converting it into the corresponding aminolactone **4** and its X-ray crystallographic analysis (vide supra).[22] Finally, the removal of the camphorsultam group of the MOM-protected **16b** under alkaline hydrolysis followed by acidic treatment gave the amino acid **20**, which, upon a three step conversion using our established method,[5] gave manzacidin B (**2**).[23]

In summary, we have developed a short and diastereoselective route to manzacidin B. The total number of processes from the aldehyde **5c** to **2**, which did not involve any oxidation-reduction sequences, included six steps and the overall yield was 48% (38% from (*R*)-α-methylserine). The key to the total synthesis was the Cu(*t*-butSal)$_2$-catalyzed isocyanoacetate aldol reaction of the aldehyde **5c** with (1*R*)-**11a** to give (4*R*,5*R*)-**16b** (13:1) in which the undesired (4*S*,5*S*)-isomer was the predominant product upon the aldol reaction of the structurally rigid aldehyde **5a** with an achiral isocyanoacetate. The Oppolzer's camphorsultam was proven to be an excellent chiral auxiliary for the diastereoselective isocyanoacetate aldol reactions even for mismatched pair double asymmetric induction. Current efforts are focused on further application of the present method for the synthesis of highly functionalized natural products having consecutive amino and hydroxy groups.

Acknowledgments

This study was supported by Grants-in-Aid (Nos. 16201045, 16073214, 18510191, 19201045, and Innovative Areas 'Chemical Biology of Natural Products') for Scientific Research from the Japan Society for the Promotion of Science (JSPS) and the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.042.

References and notes

1. (a) Scala, F.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O.; Tierney, M.; Kaiser, M.; Tasdemir, D. *Mar. Drugs* **2010**, *8*, 2162–2174; (b) Aiello, A.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O. In *Modern Alkaloids*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH, 2007; pp 271–304; (c) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2008**, *25*, 35–94; (d) Endo, T.; Tsuda, M.; Okada, T.; Mitsuhashi, S.; Shima, H.; Kikuchi, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2004**, *67*, 1262–1267; (e) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2003**, *20*, 1–48; (f) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48; (g) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113–158.
2. Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574–4576.
3. Manzacidin D. The *N*-1 methylated debromo form of manzacidin A was isolated from a fossil sponge, see: Jahn, T.; Konig, G. M.; Wright, A. D.; Worheide, G.; Reitner, J. *Tetrahedron Lett.* **1997**, *38*, 3883–3884.
4. For the total synthesis of manzacidins A and/or C: (a) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950–12951; (b) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905–5907; (c) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174–2175; (d) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930; (e) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553–1556; (f) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768–769; (g) Tran, K.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2008**, *10*, 3165–3167; (h) Ichikawa, Y.; Okumura, K.; Matsuda, Y.; Hasegawa, T.; Nakamura, M.; Fujimoto, A.; Masuda, T.; Nakano, K.; Kotsuki, H. *Org. Biomol. Chem.* **2012**, *10*, 614–622; For the synthesis of manzacidin B: (i) Sankar, K.; Rahman, H.; Das, P. P.; Bhimireddy, E.; Sridhar, B.; Mohapatra, D. K. *Org. Lett.* **2012**, *14*, 1082–1085; For the synthesis of manzacidin D: (j) Drouin, C.; Woo, J. C. S.; MacKay, D. B.; Lavigne, R. M. A. *Tetrahedron Lett.* **2004**, *45*, 7197–7199; For a review: (k) Hashimoto, T.; Maruoka, K. *Org. Biomol. Chem.* **2008**, *6*, 829–835.
5. (a) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708–10709; (b) Oe, K.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2008**, *49*, 7426–7429.
6. (a) Shinada, T.; Ikebe, E.; Oe, K.; Namba, K.; Kawasaki, M.; Ohfune, Y. *Org. Lett.* **2007**, *9*, 1765–1767; (b) Shinada, T.; Ikebe, E.; Oe, K.; Namba, K.; Kawasaki, M.; Ohfune, Y. *Org. Lett.* **2010**, *12*, 2170.
7. (a) Ito, Y.; Matsuura, T.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5781–5784; (b) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; (c) Togni, A.; Pastor, S. D. *Helv. Chim. Acta* **1989**, *72*, 1038–1042.
8. According to the transition state model proposed by Ito–Hayashi et al.,[7] the trans selectivity at C4 and C5 is derived from the enolate geometry to be *Z* and the facial selectivity either 5*R* or 5*S* is controlled by the chiral catalyst in which the internal organic base chelates to both the aldol donor and acceptor. However, the stereochemical outcome of the undesired (4*S*,5*S*)-selectivity in this case remained uncertain due to the structural complexity of the aldol acceptor **5a** which possessed an aldehyde attached to the quaternary carbon center with the sterically bulky and polar functional groups

9. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.
10. The examined catalysts (5 mol %), reaction time, and the ratio of **6**/**7** were as follows: $Cu(acac)_2$, 2 h, 1:9 (88% yield); Cu(salen), 72 h, 1:9 (85%); Cu(TPP), 2 h, 1:9 (57%); $Ag(acac)_2$, 24 h, 1:8 (52%); AuCl, 168 h, 1:6 (89%); $Pd(acac)_2$, 72 h, 1:5 (52%); without catalyst for 24 h, a trace amount of a mixture of **6**/**7** was produced (ratio not determined).
11. Preparation of **5b**, see ref 5b. Preparation of **5c**, and **11a**, **b**, see Supplementary data.
12. (a) Moon, S. –H.; Ohfune, Y. *J. Am. Chem. Soc.* **1994**, *116*, 7405–7406; (b) Alias, M.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A.; Lapena, Y. *Tetrahedron* **1998**, *54*, 14963–14974; (c) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115–1129.
13. The product's ratio was calculated from the ^{1}H NMR spectra of the mixture. The major isomers were assigned as the (4*S*,5*S*,6*R*)-isomers, **9a**, **b**, by converting them to the mixture of amino acids, **20** and its (4*S*,5*S*,6*R*)-isomer.[6b] See Supplementary data.
14. Tang, J. S.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 8750–8754.
15. (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004; (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241–1250.
16. For a recent example of the Michael reaction with camphorsultam; see Kaniskan, H. Ü.; Garner, P. *J. Am. Chem. Soc.* **2007**, *129*, 15460–15461.
17. The stereochemistry of the major product was assigned to (2*S*,3*R*)-**15** by converting it into (2*S*,3*R*)-3-hydroxyisoleucine whose spectroscopic data as well as the sign of the optical rotation were completely identical to the reported values.[18] See Supplementary data.
18. For the synthesis of the optically active 3-hydroxyleucine; (a) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274–7276; (b) Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757–1762; (c) Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663–7666; (d) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A., ; Smith, A. B., III *J. Am. Chem. Soc.* **1996**, *118*, 3584–3590. and other references cited therein..
19. The reactions of **5a**–**c** with **10a**, **b** in the presence of 5 mol % $Cu(t\text{-butSal})_2$ and 5 mol % Et_3N in 1,2-dichoroethane at room temperature for 5 min afforded a mixture of the (4*R*,5*R*)- and (4*S*,5*S*)-oxazolines. Their (4*R*,5R)- and (4*S*,5*S*)-ratios were as follows: **5a** with **10a** = 3:4 (78% yield), **5a** with **10b** = 2:3 (68%), **5b** with **10a** = 2:3 (57%), **5b** with **10b** = 1:2 (55%), **5c** with **10a** = 2:3 (81%), and **5c** with **10b** = 2:3 (62%).
20. No interconversion between the aldol products **16b** and **17b** was observed when the mixture was treated under the same reaction conditions.
21. The reaction of the acetonide **5a** with each enantiomer of the camphorsultams **11a**, **b** afforded a mixture of the corresponding aldol adducts. The ratios were as follows: **5a** with **11a**, (4*R*,5*R*)/(4*S*,5*S*)-isomer = 2:1 (51%); **5a** with **11b**, (4*R*,5*R*)/(4*S*,5*S*)-isomer = 1:20 (58%).
22. The structure revision of manzacidin B in our previous paper [6b] was guided by this study involving the X-ray structural analysis of the aminolactone **4**, and its conversion to (4*R*,5*R*,6*R*)-manzacidin (**2**) whose spectroscopic data (^{1}H and ^{13}C NMR) as well as the sign of the optical rotation were identical to those of the natural **2**. For details of the preparation of the aminolactone **4** from **16a** and its conversion to **2**, see the Supplementary data.
23. Since manzacidins A and C are configurational isomers at C6 to be either 6*S* or 6*R*, we proposed that both natural products were biosynthesized from an (*S*)-α-amino acid.[5a] Based on this hypothesis, we considered that the structure of manzacidin B would be a C5 hydroxylated form of manzacidins A or C. However, the absolute structure of manzacidin B, confirmed by our previous[6b] and present studies, suggested its possible biosynthetic pathway as follows: (i) manzacidin B was derived from an (*R*)-α-amino acid via a different biosynthetic pathway from manzacidins A and C, or (ii) its biosynthesis involved an epimerization at C4 after the hydroxylation of manzacidin C at C5 since both manzacidins B and C possessed the same (6*R*)-configuration.