Magnesium-Coordinated Chelation Control in 1,3-Dipolar Cycloaddition of Chiral α-Alkoxymethyl Ether Nitrile Oxide: Application to the Synthesis of (–)/(–)-*cis*-Clausenamide

Kazuhiro Tanda,* Atsushi Toyao, Akiko Watanabe, Masanori Sakamoto, Tetsuo Yamasaki*

Department of Pharmaceutical Chemistry, Kyushu University of Health and Welfare, 1714-1 Yoshino, Nobeoka, Miyazaki 882-8508, Japan
Fax +81(982)235711; E-mail: tanda@phoenix.ac.jp; E-mail: tetsuyam@phoenix.ac.jp

Received: 29.08.2014; Accepted after revision: 30.09.2014

Abstract: A facile regio- and diastereoselective nitrile oxide cycloaddition method using magnesium-coordinated chelation control of chiral α-alkoxymethyl ether nitrile oxide is reported. This reaction could be successfully applied as a key step in both the formal total synthesis of (–)-clausenamide and the total synthesis of (–)-*cis*-clausenamide.

Key words: cycloaddition, magnesium, nitrile oxide, diastereoselectivity, natural products

The 1,3-dipolar cycloaddition of nitrile oxides has attracted considerable attention in synthetic organic chemistry because of its application in the synthesis of complex natural products.[1] Thus, numerous examples of regio- and/or diastereoselective nitrile oxide cycloaddition reactions have been developed and intensely studied.[2] One of the major advances in this field is the metal-coordinated 1,3-dipolar cycloaddition of benzonitrile oxide with allylic alcohols in the presence of magnesium alkoxides, which introduce a high reaction rate enhancement and absolute regiocontrol, as reported by Kanemasa et al.[3] Recently, Carreira et al. have developed convenient and broadly applicable (i.e., including aliphatic nitrile oxides) reaction conditions for highly diastereoselective cycloaddition reactions by improving upon Kanemasa's methods.[4] In this contribution, we describe the regio- and diastereoselective 1,3-dipolar cycloaddition of α-alkoxy aliphatic nitrile oxides to 3-substituted allylic alcohols.

Racemic clausenamide was first isolated from *Clausena lansium* (Lours.) Skeels, a Chinese folk medicine; (–)-clausenamide (**1**) has shown potent nootropic activities in many behavioral experiments, and is currently being developed as a promising antidementia drug.[5] Moreover, (–)-*cis*-clausenamide (**2**), the C3 isomer of **1**, is demonstrated to be nearly twice as active as **1** (Figure 1).[6] Given the important pharmacological activity and interesting molecular structure — namely, a densely substituted pyrrolidinone ring with four contiguous stereocenters — it is clear why the clausenamides are widely studied by synthetic chemists as important synthetic targets.[7]

In the context of our study on 1,3-dipolar cycloaddition reactions, we succeeded in the development of a new synthetic route toward the stereocontrolled synthesis of 3,4,5-trisubstituted 2-isoxazolines, including an improvement in cycloaddition diastereoselectivity by use of a combination of alkoxymethyl ether nitrile oxides with magnesium alkoxide. This facile approach to the synthesis of substituted 2-isoxazolines was applied to both a formal total synthesis of **1** and a total synthesis of **2**.

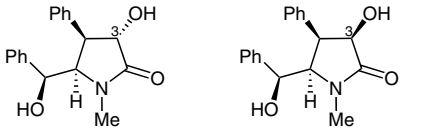
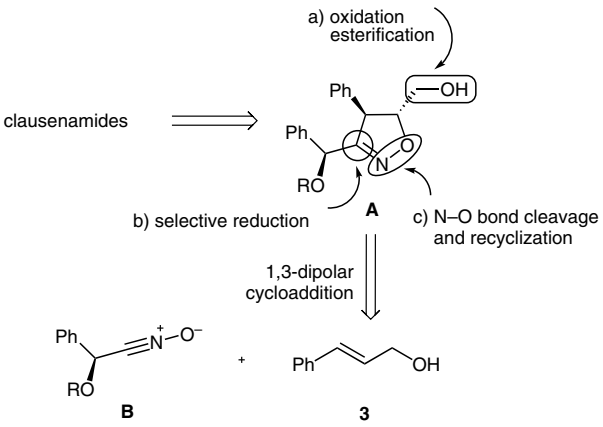


Figure 1 Structure of (–)-clausenamide (**1**) and (–)-*cis*-clausenamide (**2**)

The outline of our synthesis strategy toward the clausenamides is illustrated in Scheme 1. The clausenamides may be synthesized from 2-isoxazoline **A**, by (a) oxidation and esterification, (b) selective reduction, and (c) N–O bond cleavage and subsequent recyclization to construct the pyrrolidinone rings. 2-Isoxazoline **A** may be obtained by a putative 1,3-dipolar cycloaddition of nitrile oxide **B** with cinnamyl alcohol **3** from the less hindered face in an *exo* fashion.



Scheme 1 Retrosynthetic analysis of clausenamides

On the basis of our strategy, various chiral nitrile oxide precursors, hydroximoyl chlorides **4a**–**e**, were readily prepared from known ester L-methyl mandelate (Table 1).[8] When compound **4a** was treated with (*E*)-cinnamyl alco-

SYNLETT 2014, 25, 2953–2956
Advanced online publication: 06.11.2014
DOI: 10.1055/s-0034-1379485; Art ID: st-2014-u0725-l
© Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

hol (**3**)[9] in the presence of *i*-PrOH and EtMgBr in CH_2Cl_2 at room temperature, the cycloaddition proceeded to give a 62:38 separable mixture of cycloadduct **5a** and its diastereomer **5a'** in 69% combined yield (entry 1). Treatment of **4b** with **3** under similar conditions resulted in a decrease in diastereoselectivity to give a 54:46 mixture of **5b** and **5b'** in 80% yield (entry 2). However, when a similar reaction was carried out with **4c**, with an α-hydroxy hydroximoyl chloride and a MOM protecting group, the starting material was smoothly consumed to give a 75:25 separable mixture of **5c** and its diastereomer **5c'** in 85% yield (entry 3). When **4d**, possessing MEM substitution, was treated under similar conditions, the diastereoselectivity of the cycloaddition was slightly increased to 78:22 (entry 4). Finally, the use of toluene as a solvent with **4d** gave more satisfactory results, affording the corresponding cycloadducts in 64% yield with 87:13 diastereoselectivity (entry 5). Treatment of **4e** with **3**, to verify that the method preserves the stereochemical configuration at the benzyl position, gave the corresponding cycloadducts in 56% yield, similar to the result obtained using **4d**, without racemization (entry 6).

The significant increase in diastereoselectivity in the reactions of nitrile oxides **4c** and **4d** with cinnamyl alcohol (**3**) might be explained by considering the chelation effect between magnesium alkoxides and the MOM and MEM group of the nitrile oxide. This chelation effect, which causes a steric interaction with the phenyl group of **3** in the cycloaddition transition state, results in the cycloadduct being obtained by reaction in the less hindered *exo* mode (Figure 2).

This effect between magnesium alkoxides and α-alkoxymethyl ether nitrile oxide might be supported by an experiment in which replacing the MEM group of the nitrile oxide with an alkyl group would result in a change in diastereoselectivity. The structure of major cycloadduct **5c** was established by X-ray crystallographic analysis after further elaboration to **7**, as shown in Scheme 2. Treatment of **5c** with Dess–Martin periodinane, followed by oxidation with sodium chlorite, yielded the corresponding carboxylic acid. Subsequent methyl ester formation with TMS-diazomethane gave methyl ester **6** in 91% yield over three steps. Deprotection of **6** with acid produced the corresponding alcohol, which was esterified with 4-nitrobenzoyl chloride to give a crystalline product, ester **7**, in 90% yield.[11]

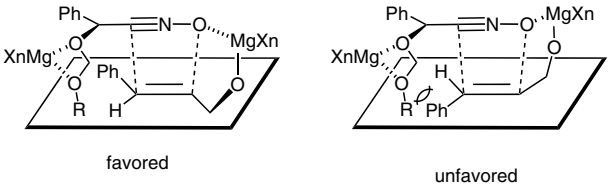
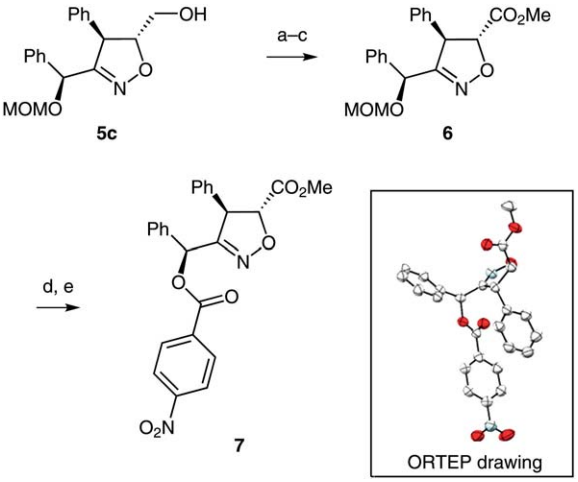
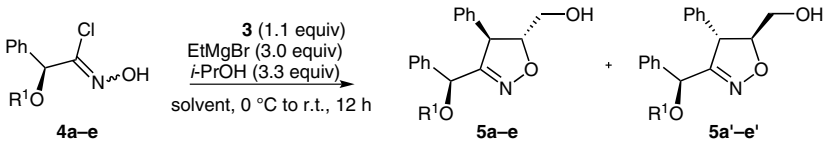


Figure 2 Stereochemical model



Scheme 2 *Reagents and conditions*: (a) Dess–Martin periodinane, CH_2Cl_2, r.t.; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O, r.t.; (c) $TMSCHN_2$, benzene–MeOH, 91% from **5c**; (d) HCl aq, THF, r.t., (e) 4-nitrobenzoyl chloride, Et_3N, CH_2Cl_2, r.t., 90% from **6**.

Table 1 1,3-Dipolar Cycloaddition of Cinnamyl Alcohol **3** with α-Hydroxy-Protected Nitrile Oxides **4a–e**[10]



Entry	**4**	R^1 (**4**)	Solvent	Cycloadducts	Yield (%)[a]	Ratio[b]
1	**4a**	TBDMS	CH_2Cl_2	**5a**/**5a'**	69	62:38
2	**4b**	*n*-propyl	CH_2Cl_2	**5b**/**5b'**	80	54:46
3	**4c**	MOM	CH_2Cl_2	**5c**/**5c'**	85	75:25
4	**4d**	MEM	CH_2Cl_2	**5d**/**5d'**	56	78:22
5	**4d**	MEM	toluene	**5d**/**5d'**	64	87:13
6	**4e**	(+)-menthoxymethyl	CH_2Cl_2	**5e**/**5e'**	56	77:23

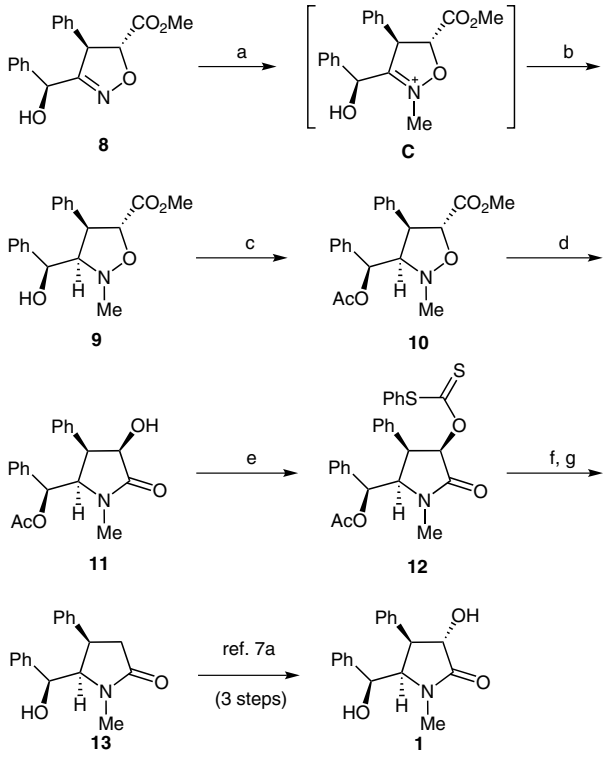
[a] Isolated yield after column chromatography.
[b] Determined by ^1H NMR spectroscopic analysis after purification.

 © Georg Thieme Verlag Stuttgart · New York

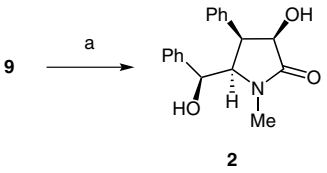
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

We then examined the elaboration of **8** to intermediate **9** en route to (–)-clausenamide (**1**) (Scheme 3). 2-Isoxazoline **8**, which was available from MOM-group cleavage of **6**, was subjected to trimethyloxonium tetrafluoroborate to give *N*-methylisoxazolinium salt **C**.[12] In our trials using several hydride-delivering reagents (data not shown) for the conversion of **C** into **9**, treatment with zinc borohydride successfully afforded **9** as a single stereoisomer in 63% yield from **8**. To our knowledge, this is the first example of a stereoselective reduction of the C=N bond of a 3,4,5-trisubstituted isoxazolinium salt.[13]

The hydroxyl group of **9** was protected as the acetate by using acetic anhydride, then reduction of **10** with zinc dust and acetic acid effected cleavage of the N–O bond followed by concomitant cyclization of the resulting amino ester to pyrrolidinone **11** in 73% yield. By using the Barton–McCombie deoxygenation protocol,[14] **11** was transformed into thionocarbonate **12**, which was then treated with tributyltin hydride and a stoichiometric amount of triethylborane to afford the deoxygenated intermediate. Subsequent treatment with LiOH gave deoxypyrrolidinone **13** in 63% yield over two steps; the latter compound is a known intermediate of (–)-clausenamide (**1**).[7a,15] Finally, reductive cleavage of **9** with zinc dust and acetic acid gave (–)-*cis*-clausenamide (**2**) in 66% yield (Scheme 4).[16]



Scheme 3 *Reagents and conditions*: (a) $(CH_3)_3BF_4$, CH_2Cl_2, r.t.; (b) $Zn(BH_4)_2$, THF, –78 °C, 63% from **8**; (c) Ac_2O, DMAP, pyridine, CH_2Cl_2, r.t.; (d) Zn, AcOH–H_2O, 90 °C, 73% from **9**; (e) *O*-phenyl chlorothionoformate, pyridine, DMAP, CH_2Cl_2, 40%; (f) Bu_3SnH, cat. Et_3B, toluene, r.t.; (g) aq LiOH, MeOH, r.t. 63% from **11**.



Scheme 4 *Reagents and conditions*: (a) Zn, AcOH–H_2O, 90 °C, 66%.

In conclusion, we have revealed that magnesium alkoxides influence not only the regioselectivity, but also the diastereoselectivity of the 1,3-dipolar cycloaddition of α-alkoxymethyl ether nitrile oxide and cinnamyl alcohol; we have used this mode of reactivity to develop a new route for the synthesis of clausenamide and derivatives. We believe that our results constitute a valuable contribution toward asymmetric 1,3-dipolar cycloaddition reactions without chiral catalysts and/or auxiliaries. The elucidation of the mechanism for the diastereoselectivity of the cycloaddition and further applications of this method to the synthesis of additional natural products are under intense investigation.

Acknowledgment

This work was financially supported by The Science Research Promotion Fund. We also thank Dr. Osamu Tamura and Dr. Tamiko Kiyotani at Showa Pharmaceutical University for X-ray analysis of **7**.

References and Notes

(1) (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719. (c) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; John Wiley and Sons: New York, **2002**. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.

(2) (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. For chiral catalysis and/or auxiliaries in nitrile oxide cycloadditions, see: (b) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075. (c) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366. (d) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349. (e) Yamamoto, H.; Hayashi, S.; Kubo, M.; Harada, M.; Hasegawa, M.; Noguchi, M.; Sumitomo, M.; Hori, K. *Eur. J. Org. Chem.* **2007**, 2859. (f) Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G.; Kündig, E. P. *Tetrahedron* **2007**, *63*, 8413. (g) Suga, H.; Adachi, Y.; Fujimoto, K.; Furihata, Y.; Tsuchida, T.; Kakehi, A.; Baba, T. *J. Org. Chem.* **2009**, *74*, 1099.

(3) (a) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324. (b) Kanemasa, S.; Okuda, K.; Yamamoto, H.; Kaga, S. *Tetrahedron Lett.* **1997**, *38*, 4095. (c) Kanemasa, S. *Synlett* **2003**, 1371.

(4) (a) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 2082. (b) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611. (c) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410. (d) Fader, L. D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2485. (e) Muri, D.; Lohse, N.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4036. (f) Becker, N.; Carreira, E. M. *Org. Lett.* **2007**, *9*, 3857.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

© Georg Thieme Verlag Stuttgart · New York

(5) (a) Chen, Y. R.; Yang, M. H.; Huang, L.; Liu, G.; Benz, U. Ger. Offen. DE3431257 Appl. Aug 24, **1984**; *Chem. Abstr.* **1986**, *105*, 72689r. (b) Feng, Z.; Li, X.; Zheng, G.; Huang, L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2112.
(6) Li, X.; Zhu, C.; Li, C.; Wu, K.; Huang, D.; Huang, L. *Eur. J. Med. Chem.* **2010**, *45*, 5531.
(7) For previous syntheses of these compounds, see: (a) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352. (b) Huang, D. F.; Huang, L. *Tetrahedron* **1990**, *46*, 3135. (c) Yakura, T.; Matsumura, Y.; Ikeda, M. *Synlett* **1991**, 343. (d) Cappi, M. W.; Chen, W.-P.; Flood, R. W.; Liao, Y.-W.; Roberts, S. M.; Skidmore, J.; Smith, J. A.; Williamson, N. M. *Chem. Commun.* **1998**, 1159. (e) Yang, L.; Wang, D.-X.; Zheng, Q.-Y.; Pan, J.; Huang, Z.-T.; Wang, M.-X. *Org. Biomol. Chem.* **2009**, *7*, 2628. (f) Zhang, L.; Zhou, Y.; Yu, X. *Synlett* **2012**, 1217. (g) Xuan, Y.-N.; Lin, H.-S.; Yan, M. *Org. Biomol. Chem.* **2013**, *11*, 1815.
(8) All hydroximoyl chlorides expect for **4d** are stable under prolonged storage.
(9) We obtained (*E*)-cinnamyl alcohol **3** by the Luche reduction of (*E*)-cinnamaldehyde, see: Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(10) **1,3-Dipolar Cycloaddition of Cinnamyl Alcohol (3) with α-Hydroxy-Protected Nitrile Oxides; Typical Procedure for 4c:** To a solution of the (*E*)-cinnamyl alcohol (**3**) (796 mg, 5.94 mmol) and *i*-PrOH (1.50 mL, 17.8 mmol) in CH_2Cl_2 (187 mL) was added EtMgBr (1.0 mol/L in THF, 17.8 mL, 17.8 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. At this time, hydroximoyl chloride **4c** (1.50 g, 6.53 mmol) in CH_2Cl_2 (100 mL) was added to the reaction dropwise by using a dropping funnel over 20 min, followed by two rinses with CH_2Cl_2 (5 mL each). The reaction mixture was stirred for 12 h and gently warmed to r.t., then the reaction was quenched with sat. aq NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column flash chromatography (hexane–EtOAc, 1:1) to give cycloadducts **5c**/**5c'** (1.81 g, 85%) as a yellow oil. d.r. = 75:25 [integration of signals at δ = 5.40 (major) and 5.28 (minor) ppm in the ^{1}H NMR spectrum]. **Major Cycloadduct 5c:** $[\alpha]_D^{27}$ –160.7 (c 1.00, $CHCl_3$). IR (film): 3428, 3060, 3028, 2945, 2889, 2825, 1604, 1494, 1455, 1151, 1094, 1035, 902, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 8 H), 7.17 (d, *J* = 6.8 Hz, 2 H), 5.40 (s, 1 H), 4.58 (dd, *J* = 5.6, 3.6 Hz, 1 H), 4.32 (dd, *J* = 60.4, 6.8 Hz, 2 H), 4.19 (d, *J* = 6.0 Hz, 1 H), 3.73–3.68 (m, 1 H), 3.59–3.53 (m, 1 H), 3.11 (s, 3 H), 1.94 (t, *J* = 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 138.4, 137.3, 129.0, 128.5, 128.3, 127.9, 127.8, 127.1, 93.8, 89.9, 72.2, 63.1, 55.7, 55.4, 53.4. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_4$: 328.1549; found: 328.1533.
(11) **Spectroscopic Data for 7:** Colorless crystals; mp 131–133 °C (from MeOH). $[\alpha]_D^{28}$ –212.9 (c 1.00, $CHCl_3$). IR (film): 3113, 3067, 3031, 2970, 2947, 2847, 1742, 1732, 1601, 1523, 1517, 1351, 1264, 1235, 1105, 1012, 851 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 9.2 Hz, 2 H), 7.42–7.17 (m, 10 H), 6.95 (s, 1 H), 4.95 (d, *J* = 4.8 Hz, 1 H), 4.48 (d, *J* = 4.4 Hz, 1 H), 3.72 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 162.7, 158.1, 150.6, 137.3, 135.1, 134.2, 130.8, 129.5, 129.1, 129.0, 128.3, 127.7, 126.0, 123.3, 86.7, 71.2, 57.1, 52.9. HRMS (FAB): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{20}N_2O_7Na$: 483.1168; found: 483.1181.
(12) For the preparation of *N*-methylisoxazolinium tetrafluoroborates, see: Cerri, A.; De Micheli, C.; Gandolfi, R. *Synthesis* **1974**, 710.
(13) For reduction of isoxazolimium salts, see: (a) Henneböhle, M.; LeRoy, P.-Y.; Hein, M.; Ehrler, R.; Jäger, V. *Z. Naturforsch., B: J. Chem. Sci.* **2004**, *59*, 451. (b) Jäger, V.; Frey, W.; Bathich, Y.; Shiva, S.; Ibrahim, M.; Henneböhle, M.; LeRoy, P.-Y.; Imerhasan, M. *Z. Naturforsch., B: J. Chem. Sci.* **2010**, *65*, 821.
(14) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. For reviews, see: (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.
(15) **Spectroscopic Data for 13:** $[\alpha]_D^{27}$ –184.1 (c 0.50, $CHCl_3$); mp 122–124 °C. IR (film) 3362, 3088, 3056, 3030, 2923, 2243, 1670, 1492, 1454, 1401, 1259, 1042, 911, 760 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.28–7.06 (m, 8 H), 6.71–6.69 (m, 2 H), 5.34 (d, *J* = 3.6 Hz, 1 H), 4.64 (dd, *J* = 2.8, 3.2 Hz, 1 H), 4.28 (dd, *J* = 3.2, 5.2 Hz, 1 H), 3.82 (dt, *J* = 8.4, 12.4 Hz, 1 H), 2.91 (s, 3 H), 2.08–1.96 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 141.2, 137.7, 128.4, 127.7, 127.3, 127.0, 126.8, 126.3, 72.1, 67.8, 40.7, 33.1, 30.1. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1494; found: 282.1522.
(16) **Synthesis of (–)-*cis*-Clausenamide (2):** A mixture of **9** (350 mg, 1.07 mmol) and zinc dust (1.05 g, 16.0 mmol) was heated at 90 °C in AcOH–H_2O (10:1, 18 mL) for 3 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc, neutralized with sat. aq $NaHCO_3$ solution and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column flash chromatography ($CHCl_3$–MeOH, 15:1) to give (–)-*cis*-clausenamide (**2**) (272 mg, 86%). $[\alpha]_D^{26}$ –6.78 (c 1.00, $CHCl_3$); mp 194–196 °C. IR (film): 3299, 3209, 3181, 2919, 2852, 1684, 1661, 1454, 1404, 1239, 1214, 1103, 1023, 953, 910 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 10 H), 4.81 (d, J = 4.8 Hz, 1 H), 4.53 (d, J = 6.8 Hz, 1 H), 4.17 (dd, J = 6.0, 0.8 Hz, 1 H), 3.84 (dd, J = 6.0 Hz, 0.8 Hz, 1 H), 3.30 (br. s, 1 H), 2.61 (s, 3 H), 2.23 (br. s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 140.6, 134.2, 130.0, 128.6, 128.2, 127.8, 126.7, 71.9, 71.8, 65.8, 47.5, 29.6. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_3$: 298.1443; found: 298.1473.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

 © Georg Thieme Verlag Stuttgart · New York

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.