ORGANIC LETTERS

2003
Vol. 5, No. 21
3839−3842

Enantioselective Total Synthesis of (+)-Azimine and (+)-Carpaine

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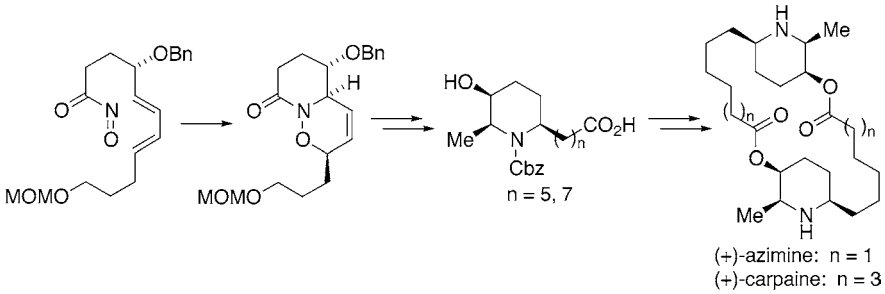
Received July 22, 2003

ABSTRACT



The enantioselective total syntheses of (+)-azimine and (+)-carpaine have been developed, starting with (*S*)-1,2,4-butanetriol as a single source of chirality. The key common feature in these syntheses involves stereoselective intramolecular hetero-Diels–Alder reaction of an acylnitroso compound. The critical macrocyclic dilactonization of the *N*-Cbz derivatives of azimic acid and carpamic acid was efficiently achieved by using the Yamguchi macrocyclization conditions.

Azimine (**1**)[1] and carpaine (**2**),[2] isolated, respectively, from *Azima tetracantha* L. and *Carica papaya* L., are a novel class of macrocyclic dilactones containing a 2,3,6-trisubstituted piperidine skeleton, and carpaine is reported to exhibit a wide range of biological properties including antitumor activity at low concentrations.[3] They are hydrolyzed to azimic acid (**3**) and carpamic acid (**4**), which are presumably their biosynthetic precursors. The structure and absolute configuration of **1**[1,4] and **2**[5,6] have been determined by spectroscopic and degradative studies. Synthetic activity in this area has resulted in numerous syntheses of azimic acid[7] and carpamic acid[8] both in racemic and enantiomeric forms, but there has been only a single report dealing with the synthesis of the macrocyclic dilactone class of alkaloid, carpaine (**2**), developed by Corey and Nicolaou.[9] This synthesis used *N*-Cbz-carpamic acid (**6**), prepared from naturally derived carpaine by *N*,*N*′-dibenzyloxycarbonylation followed by hydrolysis of the dilactone, which was recyclized via its 2-pyridinethiol ester to the bis-Cbz derivative **5** of carpaine in >50% yield.[10]

In connection with our ongoing studies on natural product synthesis based on the acylnitroso-Diels−Alder strategy,[11] we were interested in the total synthesis of azimine (**1**) and carpaine (**2**) employing this strategy. In this study, we report

(1) Rall, G. J. H.; Smalberger, T. M.; de Waal, H. L. *Tetrahedron Lett.* **1967**, *36*, 3465−3469.

(2) (a) Rapoport, H.; Baldridge, H. D., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 343−346. (b) Govindachari, T. R.; Pai, B. R.; Narasimhan, N. S. *J. Chem. Soc.* **1954**, 1847−1849.

(3) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp 89−182.

(4) Smalberger, T. M.; Rall, G. J. H.; de Waal, H. L.; Arndt, R. R. *Tetrahedron* **1968**, *24*, 6417−6421.

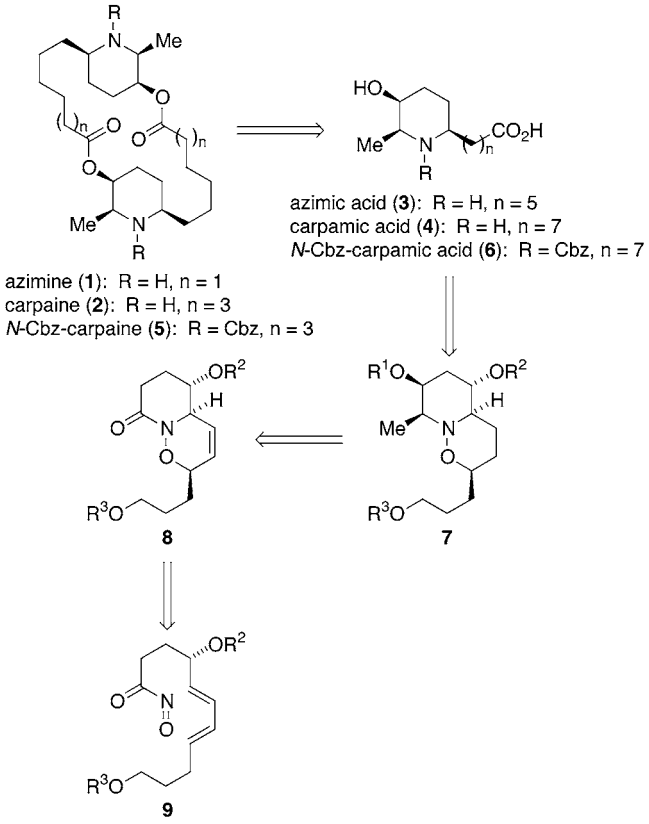
(5) (a) Govindachari, T. R.; Narasimhan, N. S. *J. Chem. Soc.* **1955**, 1563−1565. (b) Spiteller-Friedmann, M.; Spiteller, G. *Monatsh. Chem.* **1964**, *95*, 1234−1241. (c) Govindachari, T. R.; Nagarajan, K.; Viswanathan, N. *Tetrahedron Lett.* **1965**, *24*, 1907−1916.

(6) Coke, J. L.; Rice, W. Y., Jr. *J. Org. Chem.* **1965**, *30*, 3420−3422.

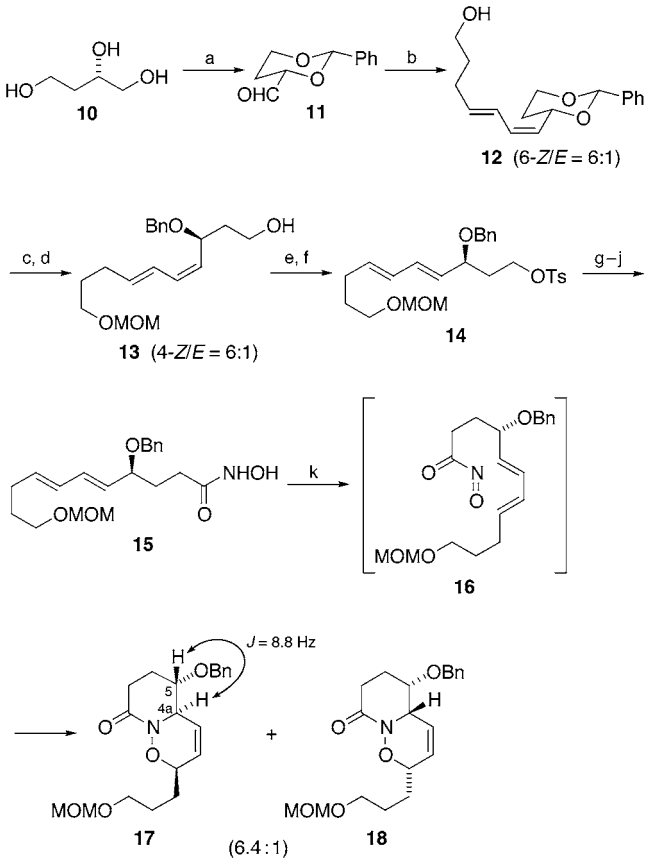
(7) For the synthesis of racemic azimic acid, see: (a) Brown, E.; Dhal, R. *Tetrhaedron Lett.* **1974**, 1029−1032. (b) Brown, E.; Dhal, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2190−2193. (c) Natsume, M.; Ogawa, M. *Heterocycles* **1980**, *14*, 169−173. (d) Hasseberg, H.-A.; Gerlach, H. *Liebigs Ann. Chem.* **1989**, 255−261. For the synthesis of (+)-azimic acid, see: (e) Hanessian, S.; Frenette, R. *Tetrahedron Lett.* **1979**, 3391−3394. (f) Lu, Z.-H.; Zhou, W.-S. *Tetrahedron* **1993**, *49*, 4659−4664. (g) Kiguchi, T.; Shirakawa, M.; Ninomiya, I.; Naito, T. *Chem. Pharm. Bull.* **1996**, *44*, 1282−1284. (h) Kiguchi, T.; Shirakawa, M.; Honda, R.; Ninomiya, I.; Naito, T. *Tetrahedron* **1998**, *54*, 15589−15606. (i) Kumar, K. K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899−13906. (j) Ma, D.; Ma, N. *Tetrahedron Lett.* **2003**, *44*, 3963−3965.

10.1021/ol030088w CCC: $25.00
Published on Web 09/23/2003

Scheme 1. Retrosynthetic Analysis of Azimine and Carpaine



Scheme 2 [a]



[a] Reagents and conditions: (a) PhCHO, TsOH, then Swern oxidation (ref 12a,b); (b) $Br^{-}Ph_3P^{+}CH_2CH{=}CHCH_2CH_2CH_2OH$, LiHMDS, THF−HMPA (2:1), rt, 66%; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 60 °C, 93%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 84%; (e) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 91%; (f) *hν*, I_2, benzene, 94%; (g) NaCN, DMSO, 50 °C, 95%; (h) NaOH, MeOH−H_2O, reflux; (i) CH_2N_2, Et_2O, 0 °C, 94% over two steps; (j) $NH_2OH{\cdot}HCl$, KOH, MeOH, 0 °C, 88%; (k) $NaIO_4$, H_2O−DMF (50:1), 0 °C, 69%.

the first total syntheses of **1** and a new approach to the total synthesis of **2** based on a route shown in Scheme 1 by using a macrocyclic dilactonization of azimic acid (**3**) and carpamic acid (**4**) (actually, their N-derivatives were to be used) and the intramolecular hetero-Diels−Alder reaction of the *N*-acylnitroso compound **9** as a key step.

Our synthesis began with (*S*)-1,2,4-butanetriol (**10**) as a single source of chirality (Scheme 2). Accordingly, **10** was converted to (*S*)-2,4-dihydroxybutanal which was protected as the benzylidene acetal **11**[12] to prevent possible racemization in the basic medium in the sequential Wittig reaction by keeping the equatorial arrangement of the 2-phenyl and 4-formyl groups intact.[13] Thus, the Wittig reaction of the aldehyde **11** with [(2*E*)-6-hydroxy-2-hexenyl](triphenyl)phosphonium bromide, using LiHMDS, produced the (4*S*)-dienol **12** (66% yield) with no epimerization as a 6:1 unseparable mixture of 6-*Z*/*E* geometrical isomers based on integration of NMR signals. After protection of the hydroxyl group as the MOM ether followed by DIBAL-H reduction, the resulting alcohol **13** (4-*Z*/*E* = 6:1) was converted to the tosylate and photoisomerized to give the pure (*E*,*E*)-isomer **14** by irradiation (I_2, benzene) with a 100 W high-pressure mercury lamp. Conversion to the hydroxamic acid **15** was then accomplished by a sequence of reactions involving nucleophilic displacement of the tosylate by cyanide ion, alkaline hydrolysis, esterification with diazomethane, and treatment with hydroxylamine. Upon oxidation of **15** with $NaIO_4$ in aqueous medium[14] at 0 °C, the in situ generated acylnitroso compound **16** underwent intramolecular Diels−Alder reaction to afford a 6.4:1 mixture of the trans and cis adducts (with respect to H4a and H5) **17** and **18** in 69% total yield. The trans

(8) For the synthesis of racemic carpamic acid, see: (a) Brown. E.; Bourgouin, A. *Chem. Lett.* **1974**, 109−112. (b) Brown, E.; Bourgouin, A. *Tetrahedron* **1975**, *31*, 1047−1051. (c) Holmes, A. B.; Swithenbank, C.; Williams, S. F. *J. Chem. Soc., Chem. Commun.* **1986**, 265−266. See also ref 7c,d. For the synthesis of (+)-carpamic acid, see: (d) Singh, R.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 7711−7715. See also ref 7e.

(9) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614−5616.

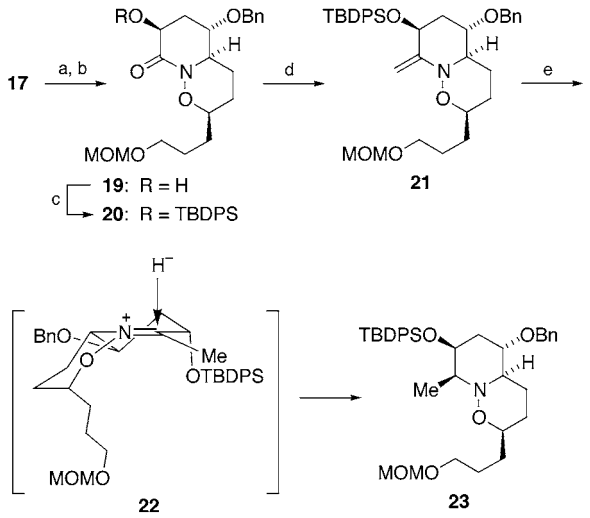
(10) Corey, E. J.; Nicolaou, K. C.; Lawrence, S.; Melvin, S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 654−655.

(11) For a review, see: (a) Kibayashi, C,; Aoyagi, S. *Synlett* **1995**, 873−879 and references therein. See also: (b) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397−8406. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592. (d) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338−3347.

(12) For the preparation of **11** from **10**, see: (a) Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *52*, 2896−2901. (b) Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83−95. See also the preparation of the antipode of **11** from (*R*)-**10**: (c) Isobe, M.; Ichikawa, Y.; Bai, D.-l.; Goto, T. *Tetrahedron Lett.* **1985**, *26*, 5203−5206. (d) Herradon, B. *Tetrahedron: Asymmetry* **1991**, *2*, 191−194.

(13) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358−1364.

Scheme 3 [a]



[a] Reagents and conditions: (a) H_2, Pd−C, THF, 97%; (b) LiHMDS, (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine, THF, −78 °C, 99%; (c) TBDPSCl, imidazole, DMF, rt, 73%; (d) MeMgBr, THF, 0 °C; (e) $NaBH_3CN$, AcOH, THF, 0 °C, 76% over two steps.

stereochemistry assigned to the major isomer **17** was based on the ^{1}H NMR coupling constant of 8.8 Hz for two vicinal protons at C4a and C5 in an axial−axial arrangement.

After catalytic hydrogenation of the olefin moiety of **17**, hydroxylation of C7 was carried out using Davis' reagent[15] according to the procedure previously developed in our group.[11d] Thus, the lactam enolate formed by treatment with LiHMDS was oxidized using (+)-[(8,8-dichlorocamphoryl)-sulfonyl]oxaziridine to furnish exclusively the (7*S*)-secondary alcohol **19** in 99% yield (Scheme 3). The desired (*S*)-configuration at the newly generated hydroxyl-bearing carbon in **19** was confirmed by ^{1}H NMR of its TBDPS ether **20**, which showed small coupling constants between equatorial H-6/H-7 (2.2 Hz) and axial H-6/H-7 (5.7 Hz) (Figure 1).

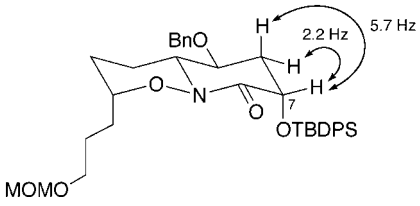


Figure 1. Assignment of the configuration of C7 of **20** based on the H−H coupling constants.

Compound **20** was treated with methylmagnesium bromide to give the enamine **21**, which was immediately reduced with $NaBH_3CN$ in acidic medium to yield the desired (8*S*)-methylated product **23** in 76% overall yield as the only stereoisomer. The required (*S*)-configuration at the newly introduced asymmetric center in **23** was unambiguously assigned on the basis of NOE correlations observed as indicated in Figure 2. The diastereoselectivity observed in this reaction can be rationalized by Stevens' stereoelectronic principle[16] in accord with the findings in our previously developed protocol[17] involving tandem Grignard reaction−reduction of transient iminium ions applied to the oxazinolactams. Thus, the exclusive selectivity in the formation of **23** can be accounted for by considering the iminium intermediate **22** which adopts the required conformation for stereoelectronic controlled axial addition of hydride from the less hindered β-face.

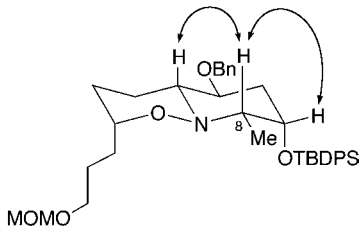


Figure 2. Assignment of the configuration at C8 of **23** based on NOE correlations.

Reductive N−O bond cleavage (Zn, 90% AcOH) of **23** provided the amino alcohol **24**, which was converted into the diol **25** in 45% overall yield via hydrogenolytic removal of the benzyl protecting group, benzyloxycarbonylation to give the tri-*N*,*O*,*O*′-Cbz derivative, and then saponification (Scheme 4). Transformation of **25** into **27** was accomplished via the thionocarbonate **26** using the Barton−McCombie deoxygenation reaction.[18] Subsequent deprotection of the MOM group and PDC oxidation followed by removal of the silyl protecting group led to the formation of the *N*-Cbz-protected azimic acid **29**. Hydrogenolytic removal of the Cbz group from **29** provided (+)-azimic acid (**3**): mp 212−215 °C (lit.[7e] mp 214−215 °C); $[\alpha]^{23}_D$ +7.45 (*c* 0.49, MeOH) [lit.[7e] $[\alpha]_D$ +8.00 (MeOH)].

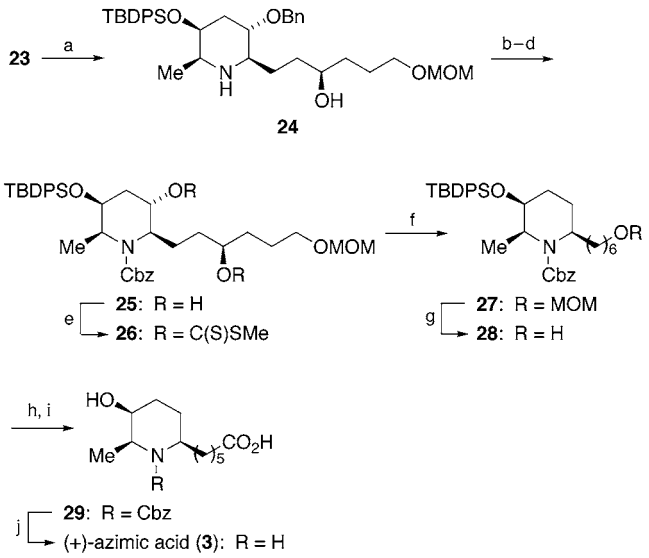
Macrocyclic dilactonization of *N*-Cbz-azimic acid (**29**) obtained was initially attempted by means of the Corey−Nicolaou protocol,[10] which had been applied to the dilactonization of *N*-Cbz-carpamic acid (**6**) as described above. Thus, **29** (9.4 mM solution in xylene) was treated with 2,2-dipyridyl disulfide (2 equiv) and triphenylphosphine (2 equiv) at reflux (48 h) to afford (+)-*N*-Cbz-azimine (**30**), but in low yield (29%). The cyclization of **29** was best effected using the Yamaguchi method[19] via an azimic 2,4,6-trichlorobenzoic mixed anhydride under high dilution conditions (2.0 mM in toluene, reflux, 36 h) to generate **30** in 71% yield (Scheme 5). Hydrogenolytic deprotection of the Cbz

(14) Enhancement of the trans stereoselectivity of aqueous intramolecular Diels−Alder reaction of acylnitroso compounds: Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 595−598.

(15) Reviews: (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934.

(16) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193−198.

Scheme 4 [a]

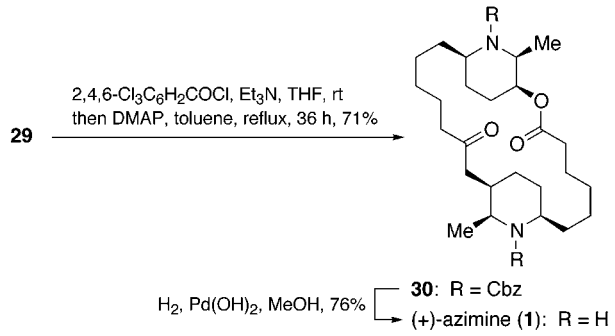


[a] Reagents and conditions: (a) Zn, 90% AcOH, 60 °C, 93%; (b) H_2, $Pd(OH)_2$, MeOH; (c) CbzCl, Na_2CO_3; (d) 1 M NaOH, MeOH, rt, 45% from **24**; (e) CS_2, NaH, imidazole, THF, reflux, then MeI, reflux, 93%; (f) Bu_3SnH, AIBN, benzene, reflux, 99%; (g) PPTS, *t*-BuOH, reflux, 73%; (h) PDC, MS 4A, DMF, rt; (i) Bu_4NF, THF, rt, 82% over two steps; (j) H_2, Pd−C, MeOH, 99%.

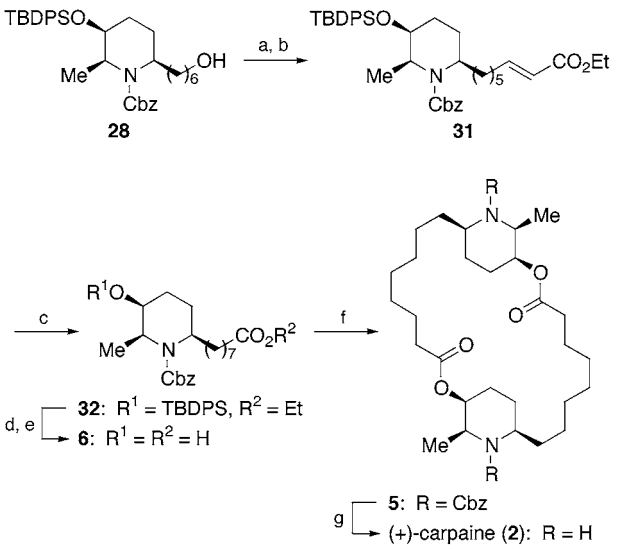
group provided (+)-azimine (**1**) as a white crystalline solid, mp 111−112 °C (lit.[1] mp 112.0−113.0 °C), whose ^{1}H NMR and MS spectral data were identical to those reported for the natural compound.[4] The specific rotation, $[\alpha]^{23}_D$ +3.14 (*c* 0.74, EtOH), of the synthetic **1**, however, was different from that reported for the natural product, $[\alpha]^{20}_D$ 0 (*c* 0.8, EtOH).[1] The discrepancy in the optical rotations may be the result of probable contamination of the sample of the natural product by a chiral impurity and/or attributed to an error incurred in the rotation measurement.

Having established an efficient macrocyclic dilactonization using the Yamaguchi method, we next sought to use this method for the synthesis of (+)-carpaine (**2**) via *N*-Cbz-carpamic acid (**6**). Starting from **28** used in the synthesis of (+)-azimine (**1**), the protected carpamic acid ester **32** was synthesized via a three-step sequence consisting of Swern

Scheme 5



Scheme 6 [a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 0 °C; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −20 °C, 91% over two steps; (c) H_2, PrO_2, AcOEt, 76%; (d) Bu_4NF, THF, rt, 97%; (e) $Ba(OH)\cdot 8H_2O$, MeOH, rt, 97%; (f) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, rt, then DMAP, toluene, reflux, 71%; (g) H_2, $Pd(OH)_2$, MeOH, 87%.

oxidation, Horner−Wadsworth−Emmons homologation, and olefin hydrogenation (Scheme 6). After deprotection of the silyl protecting group and ester hydrolysis, dilactonization of the resultant *N*-Cbz-carpamic acid (**6**) under the Yamaguchi macrocyclization conditions provided *N*-Cbz-carpaine (**5**) in 71% yield. Subsequent deprotection of the Cbz group led to the target (+)-carpaine (**2**) as a white crystalline solid: mp 119−120 °C (lit.[2a] mp 119−120 °C; lit.[6] mp 118−120 °C); $[\alpha]^{22}_D$ +20.9 (*c* 0.34, EtOH) [lit.[2a] $[\alpha]^{21}_D$ +24.7 (*c* 1.07, EtOH); lit.[28] $[\alpha]^{20}_D$ +21.4 (*c* 1.08, EtOH)], exhibited ^{1}H NMR data identical with that of reported[5c] for the natural product.

In summary, we have developed the enantioselective total syntheses of (+)-azimine (**1**) and (+)-carpaine (**2**), starting with (*S*)-1,2,4-butanetriol as a single source of chirality. The key common feature in these syntheses involves stereoselective intramolecular hetero-Diels−Alder reaction of an acylnitroso compound. The critical macrocyclic dilactonization of the *N*-Cbz derivatives of azimic acid and carpamic acid was efficiently achieved by using the Yamguchi macrocyclization conditions.

Supporting Information Available: Characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL030088W

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(18) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(19) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.