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

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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 acid⁷ and carpamic acid⁸ 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*-Cbzcarpamic 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

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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

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^{*a*} Reagents and conditions: (a) PhCHO, TsOH, then Swern oxidation (ref 12a,b); (b) Br⁻Ph₃P⁺CH₂CH=CHCH₂CH₂CH₂OH, LiHMDS, THF–HMPA (2:1), rt, 66%; (c) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, 60 °C, 93%; (d) DIBAL-H, CH₂Cl₂, 0 °C, 84%; (e) TsCl, Et₃N, DMAP, CH₂Cl₂, rt, 91%; (f) $h\nu$, I₂, benzene, 94%; (g) NaCN, DMSO, 50 °C, 95%; (h) NaOH, MeOH–H₂O, reflux; (i) CH₂N₂, Et₂O, 0 °C, 94% over two steps; (j) NH₂OH·HCl, KOH, MeOH, 0 °C, 88%; (k) NaIO₄, H₂O–DMF (50:1), 0 °C, 69%.

aldehyde 11 with [(2E)-6-hydroxy-2-hexenyl](triphenyl)phosphonium bromide, using LiHMDS, produced the (4S)-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 (I₂, 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 NaIO₄ in aqueous medium¹⁴ 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

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^{*a*} Reagents and conditions: (a) H₂, 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) NaBH₃CN, AcOH, THF, 0 °C, 76% over two steps.

stereochemistry assigned to the major isomer **17** was based on the ¹H 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' reagent¹⁵ 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 ¹H 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



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

NaBH₃CN 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 principle¹⁶ in accord with the findings in our previously developed protocol¹⁷ 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.

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} [α]_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 method¹⁹ 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

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^{*a*} Reagents and conditions: (a) Zn, 90% AcOH, 60 °C, 93%; (b) H₂, Pd(OH)₂, MeOH; (c) CbzCl, Na₂CO₃; (d) 1 M NaOH, MeOH, rt, 45% from **24**; (e) CS₂, NaH, imidazole, THF, reflux, then MeI, reflux, 93%; (f) Bu₃SnH, AIBN, benzene, reflux, 99%; (g) PPTS, *t*-BuOH, reflux, 73%; (h) PDC, MS 4A, DMF, rt; (i) Bu₄NF, THF, rt, 82% over two steps; (j) H₂, 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 ¹H 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*-Cbzcarpamic 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





^{*a*} Reagents and conditions: (a) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, $-78 \rightarrow 0$ °C; (b) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, -20 °C, 91% over two steps; (c) H₂, PrO₂, AcOEt, 76%; (d) Bu₄NF, THF, rt, 97%; (e) Ba(OH)•8H₂O, MeOH, rt, 97%; (f) 2,4,6-Cl₃C₆H₂COCl, Et₃N, THF, rt, then DMAP, toluene, reflux, 71%; (g) H₂, 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 ¹H 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.

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