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Oxazoline *N*-Oxide Mediated [2 + 3] Cycloadditions. Application to a Formal Synthesis of (+)-Carpetimycin A

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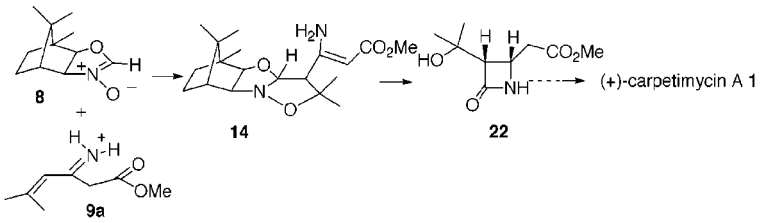
ABSTRACT



Cycloaddition between γ,δ-unsaturated β-enamino ester 9 and camphor-derived oxazoline *N*-oxide 8 afforded a single adduct, 14. Dipolarophile 9 proved to be very reactive despite the substitution on the double bond. Stereoselective sodium cyanoborohydride reduction of the imminium intermediate 14a gave rise stereoselectively to β-amino ester derivative 15a. Oxidative acidic hydrolysis, oxidation of the resulting aldehyde 18, deprotection, and cyclization afforded the β-lactam 23, a direct precursor of (+)-carpetimycin A.

Carpetimycins A and B (**1** and **2**) are isolated from fermentation broth of *Streptomyces* sp. KC-6643; they exhibit a strong activity against Gram-positive and Gram-negative bacteria and show a good resistance to β-lactamase-producing strains.[1] These antibiotics belong to the class of carbapenem antibiotics and are structurally related to thienamycin **3**.[2] However, carpetimycins A and B (**1** and **2**) are characterized by a *cis* relationship between C5-H and C6-H and by the presence of a tertiary alcohol or its sulfated ester on the C6 side chain (Figure 1).

Despite its powerful biological activity, carpetimycin A (**1**) has been the subject of only a few diastereo- or enantioselective syntheses.[3] We report in the present paper a novel formal stereoselective synthesis of this antibiotic.

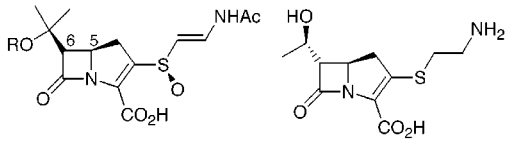


Figure 1.

Our strategy is based on the use of a new asymmetric [2 + 3] cycloaddition[4] and is presented in the retrosynthetic Scheme 1.

In the original planed strategy (path a), cycloaddition between oxazoline *N*-oxide **8** and 3-methyl-2-butenenitrile

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(1) Nakayama, M.; Kimura, S.; Tanabe, S.; Mizoguchi, T.; Watanabe, I.; Mori, T.; Miyahara, K.; Kawasaki, T. *J. Antibiot.* **1981**, *34*, 818−823.

(2) Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491−6499.

(3) Diastereoselective syntheses: (a) Ihara, M.; Konno, F.; Fukumoto, K.; Kametani, T. *Heterocycles* **1983**, *20*, 2181−2184. (b) Buynak, J. D.; Narayana Rao, M. *J. Org. Chem.* **1986**, *51*, 1571−1574. Enantioselective syntheses: (c) Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1659−1660. (d) Shibasaki, M.; Ishida, Y.; Okabe, N. *Tetrahedron Lett.* **1985**, *26*, 2217−2220.

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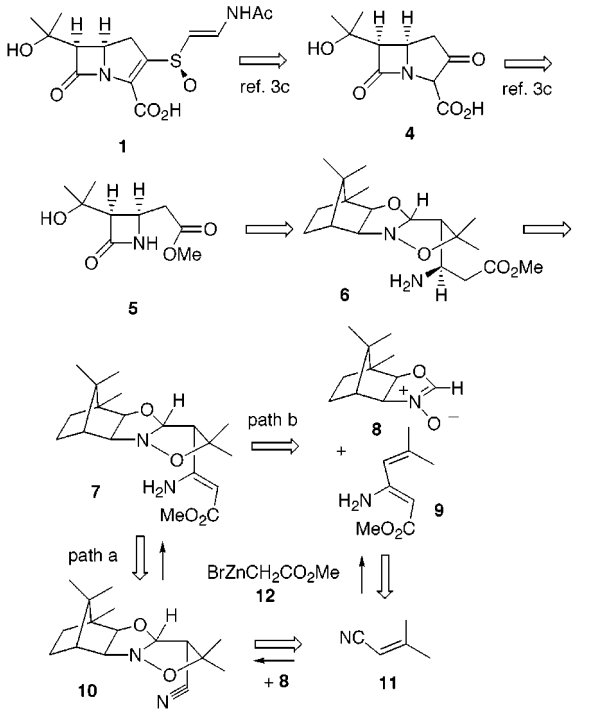
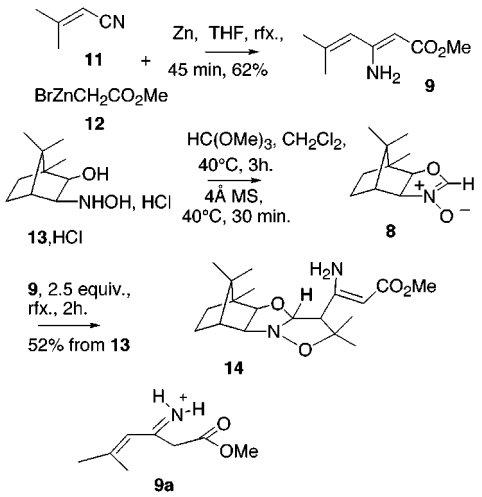
Scheme 1



(**11**) would lead to adduct **10**. A Blaise condensation between **10** and the Reformatsky reagent **12** should give rise to enamino ester **7**. Stereoselective reduction of the enamino ester double bond in **7** affording **6** should allow the introduction of the additional stereogenic center. However, this approach was thwarted by the poor reactivity of dipolarophile **11** and the lack of stereoselectivity in this particular cycloaddition.[5,6] This drawback has been overcome by the use of a more reactive dipolarophile, cyanomethylenecyclopropane, in which the cyclopropyl surrogate is a precursor of the *gem*-dimethyl group.[5] The possibility of an alternate pathway, b, in which the Blaise condensation is performed before and not after cycloaddition as in the original path a, and the unexpected reactivity of dipolarophile **9** led us to develop the more convergent strategy which is presented below.

The requisite dipolarophile **9** was prepared in 62% yield by condensation between the Reformatsky reagent **12** and nitrile **11** in refluxing THF, according to the modified Blaise reaction conditions.[7,8] Following the previously described procedure,[4] dipole **8** was obtained by condensation of hydroxylamino isoborneol hydrochloride **13** with trimethyl orthoformate[9] and was used without isolation. Cycloaddition between **9** and **8** proceeded smoothly at 40 °C and afforded after 2 h the single adduct **14** in 52% yield (Scheme 2).

Scheme 2



The high reactivity of dipolarophile **9** in which a trisubstituted double bond is engaged in cycloaddition is worthy of note. Since hydroxylamino isoborneol **13** was used as its hydrochloride, a possible equilibrium between this salt and dipolarophile **9** could lead to the more reactive imminium **9a**. Indirect proof of this possible Brönsted acidic activation was given in the following observation: when 1 equiv of triethylamine was added to the reaction medium, cycloaddition was almost suppressed. The *exo* selectivity of this cycloaddition[10] was established by X-ray analysis, after reduction of the enamino ester double bond in **14** and sulfonation to give the crystalline compound **18** (Scheme 3, vide infra).

Enamide reduction in compound **14** was performed with sodium cyanoborohydride in an acidic medium.[11,12] Diastereoselectivity is highly dependent on both solvent and

(4) (a) For a recent application to β-lactone synthesis, see: Dirat, O.; Kouklovsky, C.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 6634−6642 and references therein. (b) Dirat, O.; Kouklovsky, C.; Langlois, Y. *Org. Lett.* **1999**, *1*, 753−755. (c) Dirat, O.; Kouklovsky, C.; Langlois, Y.; Lesot, P.; Courtieu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3197−3207. (d) For a review on oxazoline *N*-oxides [2 + 3] cycloadditions, see: Langlois, Y. *Curr. Org. Chem.* **1998**, *2*, 1−18. (e) For a review on asymmetric 1,3-dipolar cycloadditions, see: Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−903.

(5) For the use of cyanomethylenecyclopropane in [2 + 3] and [2 + 4] cycloadditions, see: Mauduit, M.; Kouklovsky, C.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 6857−6860.

(6) [2 + 3] cycloaddition between methyl 3-methyl 2-butenoate and nitrile oxide can be performed under forced conditions (large excess of dipolarophile, 130−140 °C, 6.5 h), see ref 3a.

(7) Blaise reaction: (a) Blaise, E. E. *C.R. Acad. Sci.* **1901**, *132*, 478, 978. (b) Cason, J.; Rinehart, K. L., Jr.; Thornton, S. D., Jr. *J. Org. Chem.* **1953**, *18*, 1594−1600. (c) Kagan, H. B.; Suen, Y.-H. *Bull. Soc. Chim. Fr.* **1966**, 1819−1822. (d) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833−3835. (e) Syed, J.; Förster, S.; Effenberger, F. *Tetrahedron: Asymmetry* **1998**, *9*, 805−815. (f) Lee, A. S.-Y.; Cheng, R.-Y.; Pan, O.-G. *Tetrahedron Lett.* **1997**, *38*, 443−446.

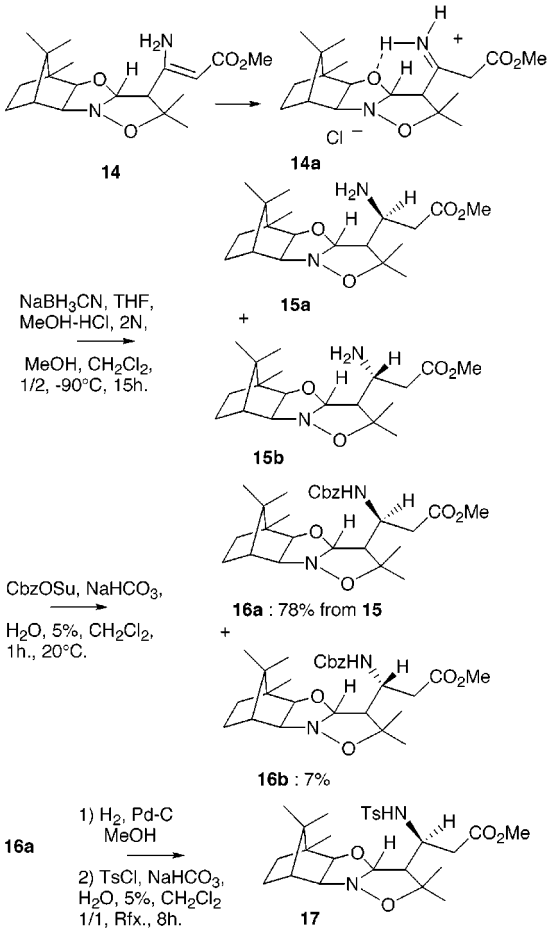
(8) For a recent preparation of enamino esters, see: (a) Fustero, S.; de la Torre, M. G.; Jofré, V.; Pérez Carlon, R.; Navarro, A.; Fuentes, A. S.; Carrio, J. S. *J. Org. Chem.* **1998**, *63*, 8825−8836 and references therein. (b) Fustero, S.; Diaz, M. D.; Navarro, A.; Salavert, E.; Aguilar, E. *Tetrahedron Lett.* **1999**, *40*, 1005−1008.

(9) Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1984,** *49*, 3127−3133.

(10) Oxazoline *N*-oxide mediated [2 + 3] cycloadditions are genarally *endo* selective. An *exo* adduct was nevertehless obtained during cycloaddition with cyclopentadiene as dipolarophile as observed in other [2 + 3] cycloadditions with this particular dienophile, see: Berranger, T.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 5523−5526.

(11) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897−2904. (b) For a review concerning the use of sodium cyanoborohydride, see: Lane, C. F. *Synthesis* **1975**, 135−146.

Scheme 3



temperature. The best result was obtained in a mixture of dichloromethane−methanol−2 N HCl at −80 °C. Under this condition, a mixture of β-amino esters **15a**,**b** was isolated in a diastereomeric excess of 80% as estimated by ^{1}H NMR. Chromatographic purification was performed following nitrogen protection as its benzyl carbamate. Following these two steps, the major carbamate derivative **16a** was isolated in 78% yield and the minor isomer **16b** in 7% yield (Scheme 3). Hydrogenolysis of compound **16a** followed by treatment with TsCl afforded after purification compound **17**. X-ray analysis of a single crystal of **17** secured the configurations of the two asymmetric centers obtained sequentially after cycloaddition and reduction (Figure 2).[13]

The diastereoselectivity of the reduction step can be explained by a preferred conformation in imminium **14a** in which the side chain could be oriented by hydrogen bonding between the imminium hydrogen and the oxygen of the oxazolidino ring system. The presence of a *gem*-dimethyl unit disfavors hydride attack on the *si* face of the imminium intermediate **14a** and led to the preferential formation of **15a** (Scheme 3).

(12) Attempted catalytic hydrogenation of the enamino ester double bond in **14** (H_2, Pd−C, MeOH) induced isomerization from *Z* to *E* without any reduction.

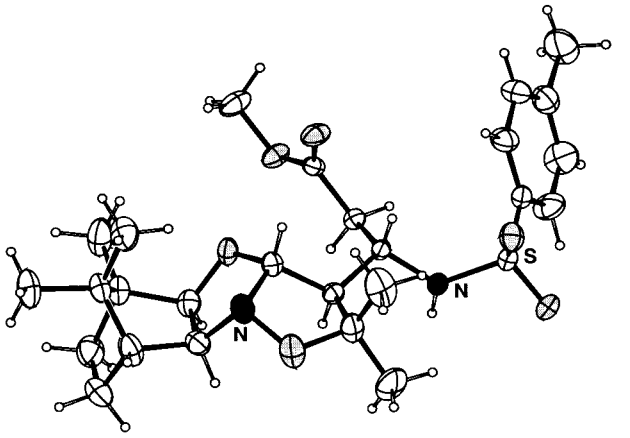
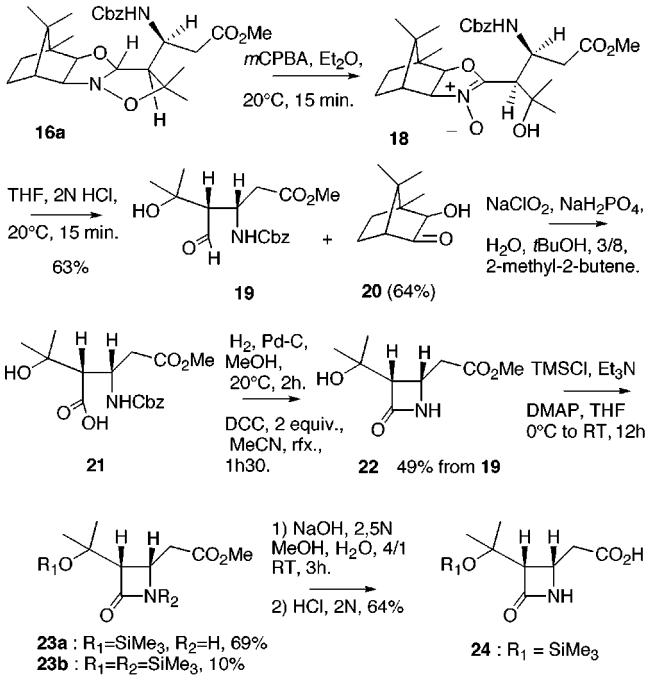


Figure 2.

Oxidative hydrolysis of compound **16a** was performed in a two-step sequence without isolation of the nitrone intermediate **18**.[4] After aqueous acidic hydrolysis, β-aminoaldehyde **19** and ketol **20**[14] were isolated, both in 64% yield. The aldehyde group in compound **19** was in turn oxidized into β-urethane acid derivative **21**.[15,16] Deprotection of the benzyloxycarbonyl group required an excess of palladium on charcoal (1.9 equiv). Final cyclization affording the β-lactam derivative **22** was performed with dicyclohexylcarbodiimide in acetonitrile (Scheme 4).[15] The coupling

Scheme 4



constant between C_3-H and C_4-H (J = 5.3 Hz) in β-lactam **22** is characteristic of a *cis* relationship between these two protons.

Moreover, compound **22** has been identified with β-lactam **24**, a synthetic precursor of carpetimycin A (**1**).[3c] Accordingly, treatment of **22** with trimethylsilyl chloride afforded a mixture of mono- and diprotected β-lactams **23a** and **23b** (Scheme 4). Saponification of the ester group in **23a** gave rise after careful acidification to compound **24**, which proved to be identical in all respects with the compound described by Ohno[3c] except for the sign of the optical rotation.

The synthesis of an enantiomeric precursor of natural (−)-carpetimycine A (**1**) is due to the unexpected *exo* selectivity in [2 + 3] cycloadditions. As both enantiomeric camphor-derived oxazoline *N*-oxides **8** are available, the natural series can be obviously obtained by a similar strategy starting from (+)-camphor as the chiral auxiliary.

This synthesis shows a new aspect of the usefulness of camphor-derived oxazoline *N*-oxide and discloses the particular reactivity of γ,δ-unsaturated enamino esters in this [2 + 3] cycloaddition. The diastereoselective introduction of a new asymmetric center on a side chain is also of interest. Further applications of this strategy in the synthesis of a more complicated carbapenem such as β-methylthienamycin are in progress in our laboratory.

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Supporting Information Available: Detailed experimental procedures and characterization data for compounds **14**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Crystal data: C_{26} H_{38} N_2 O_6 S, M_w = 506.64, colorless crystal of 0.4 × 0.3 × 0.2 mm, monoclinic, space group $P2_1$, Z = 4, a = 14.861(4) Å, b = 10.511(2) Å, c = 18.714(6) Å, β = 111.88(2)°, V = 2712.6(12), d_{calc} = 1.241 g cm^{-3}, F(000) = 1088, λ = 0.71070 Å (Mo Kα), μ = 0.161 mm^{-1}, Nonius kappa CCD diffractometer, θ range 2.20−27.43°, 48020 collected reflections, 12241 unique (R_{int} = 0.052), 9549 observed ($I > 2\sigma(I)$, full-matrix least-squares (SHELXL93[13b,c]), R = 0.0613 for 9549 observed reflections, wR_2 = 0.1153 for 12241 unique reflections, goodness of fit = 1.089, residual electron density between −0.248 and 0.258 e Å^{-3}. Absolute configuration established by examination of Bijvoet pairs. Hydrogen atoms fitted at theoretical positions. (b) Sheldrick, G. M. SHELXL93. Program for the refinement of crystal structures. University of Göttingen, Germany, 1993. (c) Crystallographic data for compound **17** has been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. (CCDC 139126).

(14) Ketol **20** can be transformed into hydroxylamino isoborneol **13** and reused, see: Berranger, T.; Langlois, Y. *J. Org. Chem.* **1995**, *60*, 1720−1726.

(15) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.

(16) For a review concerning the stereoselective preparation of β-amino acids, see: Dole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582.