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Synthesis of Maremycins A and D_1 via Cycloaddition of a Nitrone with (*E*)-3-Ethylidene-1-methylindolin-2-one

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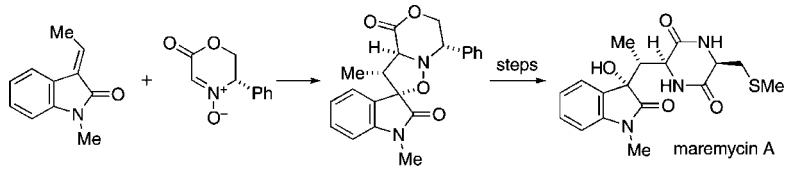
ABSTRACT



A concise synthesis of maremycins A and D_1 has been accomplished via cycloaddition of a chiral cyclic nitrone with (*E*)-3-ethylidene-1-methylindolin-2-one as a key step. This synthesis clarifies the stereochemistry of the maremycins and is suitable for large-scale synthesis for biological screening.

Maremycins A (**1**) and B (**2**) are diketopiperazine alkaloids isolated from the culture broth of marine *Streptomyces* species B 9173 (Figure 1).[1] The stereochemistries of **1** and **2** were tentatively proposed to be as depicted in Figure 1 on the basis of molecular mechanics calculations and spectroscopic data. An inseparable 1:1 mixture of maremycins C_1 (**3**) and C_2 (**4**) was obtained from *Streptomyces* sp. GT 051237, together with an inseparable 3:1 mixture of maremycins D_1 (**5**) and D_2 (**6**).[2] The stereochemistries of **3** and **4** were deduced by comparison of the NMR spectroscopic data with those of **2**, while the stereostructures of **5** and **6** were assigned by comparison of the spectra with those of **1** and **2**. Therefore, confirmation of the stereostructure of maremycins A (**1**) and B (**2**) would also establish the stereochemistries of **3**−**6**.

We have now accomplished the first synthesis of maremycins A (**1**) and D_1 (**5**) and confirmed their stereostructures to be as depicted in Figure 1.

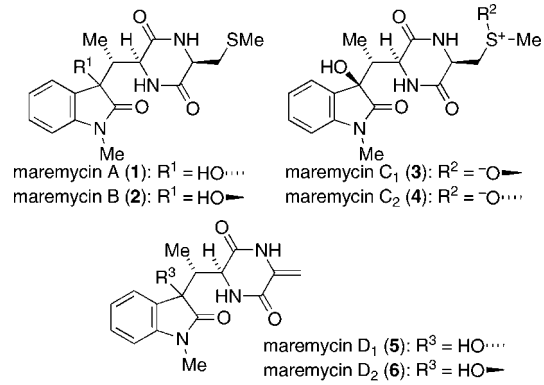


Figure 1. Proposed structures of maremycins.

The retrosynthetic analysis was as follows (Scheme 1). Maremycin D_1 (**5**) may be obtained from maremycin A (**1**) by *syn*-elimination of a sulfoxide derived from **1**. Disconnection of the diketopiperazine ring of **1** provides two amino acids, *S*-methyl-L-cysteine (**8**) and an unusual amino acid **7** that possesses three contiguous stereogenic centers, including

(1) Balk-Bindseil, W.; Helmke, E.; Weyland, H.; Laatsch, H. *Liebigs Ann.* **1995**, 1291–1294.

(2) Tang, Y.; Sattler, I.; Thiericke, R.; Grabley, S. *Eur. J. Org. Chem.* **2001**, 261–267.

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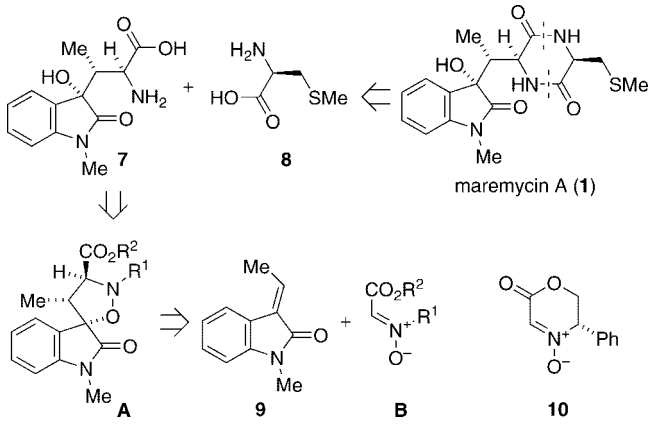
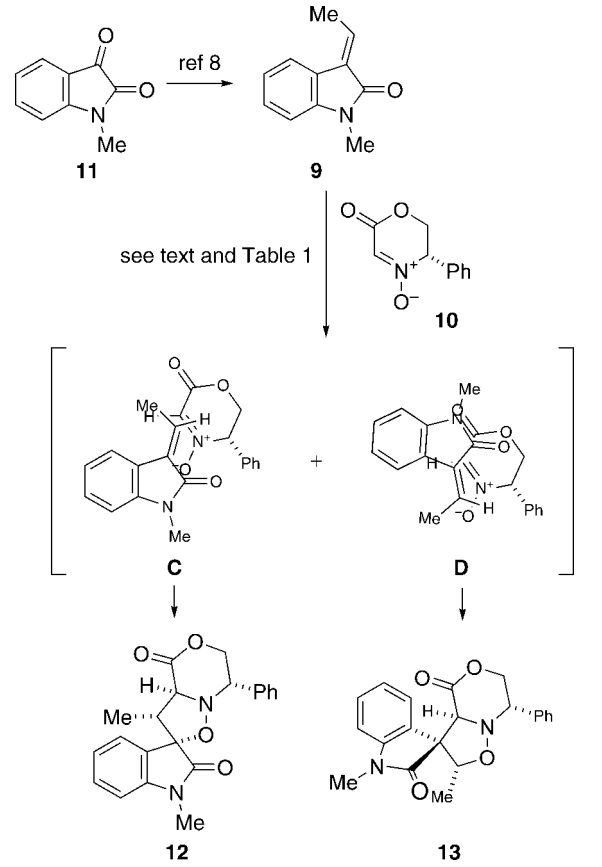
Scheme 1. Retrosynthetic Analysis of Maremycin A (**1**)



a tertiary hydroxyl group at the 3-position (indoline numbering). The latter amino acid **7** would be available by reductive cleavage of the N−O bond of spiro-(indoline isoxazolidine) **A**, which might be formed by 1,3-dipolar cycloaddition of nitrone **B** with (3*E*)-3-ethylidene-1-methylindolin-2-one (**9**). Unlike azomethine ylides, a nitrone rarely undergoes cycloaddition with a 2-oxoindolin-3-ylidene, probably because of low reactivity.[3–6] However, we considered that the nitrone template **10**,[7a,b] obtained from (*S*)-phenylglycinol within four steps, corresponding to **B** might undergo cycloaddition with **9** because of the higher reactivity of **10** as a 1,3-dipole, compared with usual nitrones.[7]

Our investigation was initiated by preparation of (*E*)-3-ethylidene-1-methylindolin-2-one (**9**) from *N*-methylisatin

Scheme 2. Cycloaddition of Indolinone **9** with Nitrone **10**



(**11**) using López-Alvarado's conditions (Scheme 2).[8] The crucial cycloaddition of 3-ethylideneindolin-2-one **9** with cyclic nitrone **10** was next examined. The cycloaddition proceeded in toluene at 60 °C for 48 h to give a 22:78 mixture of cycloadduct **12** and its regioisomer **13** in 94% yield. It should be noted that only two of the possible eight isomers were obtained, suggesting that the reaction occurs via less hindered side attack of nitrone **10** with the endo-oriented carbonyl group of the dipolarophile **9** (see **C** and **D** in Scheme 2, as well as eq 1 in Scheme 3).[7d] The stereostructures of cycloadducts **12** and **13** were determined by X-ray diffraction analysis (for **12**) and examination of the NOE difference spectra (for **13**) (Supporting Information). It is worth noting that cycloadduct **12** has all elements, including the three contiguous stereogenic centers, required for the synthesis of amino acid **7**.

Unfortunately, the desired cycloadduct **12** was the minor isomer, so we further examined the reaction conditions. To shorten the reaction time, neat conditions at various reaction temperatures were first investigated (Table 1, entries 1−3). Unexpectedly, it was found that higher reaction temperature gave a higher ratio of cycloadduct **13**. Thus, reaction of nitrone **10** with **9** at −25 °C afforded a 47:53 mixture of **12** and **13** (entry 1), whereas reaction at 60 °C gave a 22:78 mixture (entry 3). Since a kinetically controlled reaction

(3) Raunak reported that *N*-phenyl-C-substituted phenyl nitrones undergo cycloaddition with ethyl 2-oxo-3(2*H*)-indolylidene acetate under microwave irradiation conditions. The use of conventional thermal conditions was much less effective. See: Raunak, R.; Kumar, V.; Mukherjee, S.; Poonam; Prasad, A. K.; Olsen, C. E.; Schaeffer, S. J. C.; Sharma, S. K.; Watterson, A. C.; Errington, W.; Parmar, V. S. *Tetrahedron* **2005**, *61*, 5687–5697. To our knowledge, this is the only report that refers to cycloaddition of a nitrone with an indolyl-3-ylidene-2-one compound.

(4) For selected examples of cycloaddition of azomethine ylide with 3-ylideneindolin-2-ones, see: (a) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1–4. (b) Nyerges, M.; Gajdics, L.; Szollosy, A.; Toke, L. *Synlett* **1999**, 111–113. (c) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667. (d) Muthusamy, S.; Babu, S. A.; Nethaji, M. *Tetrahedron* **2003**, *59*, 8117–8127. (e) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137. (f) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086. (g) Ding, K.; Wang, G.; Deschamps, J. R.; Parrish, D. A.; Wang, S. *Tetrahedron Lett.* **2005**, *46*, 5949–5951. (h) Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 6809–6813.

(5) For examples of nitrile oxides, see: (a) El-Ahl, A. A. S. *Pol. J. Chem.* **1997**, *71*, 27–31. (b) Risitano, F.; Grassi, G.; Foti, F.; Bruno, G.; Rotondo, A. *Heterocycles* **2003**, *60*, 857–863.

(6) For examples of trimethylenemethane, see: (a) Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am. Chem. Soc.* **2007**, *129*, 3086–3087. (b) Trost, B. M.; Cramer, N.; Silverman; Steven, M. *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397.

(7) (a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun.* **1996**, 1861–1862. (b) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2000**, *65*, 8544–8551. (c) Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Commun.* **2003**, 2678–2679. (d) Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 4569–4577. (e) See also Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819–6822. (f) Long, A.; Baldwin, S. W. *Tetrahedron Lett.* **2001**, *42*, 5345.

(8) López-Alvarado, P.; Avendaño, C. *Synthesis* **2002**, 104–110.

Table 1. Cycloaddition of Nitrone **10** with 3-Ethylidene-1-methylindolin-2-one (**9**)

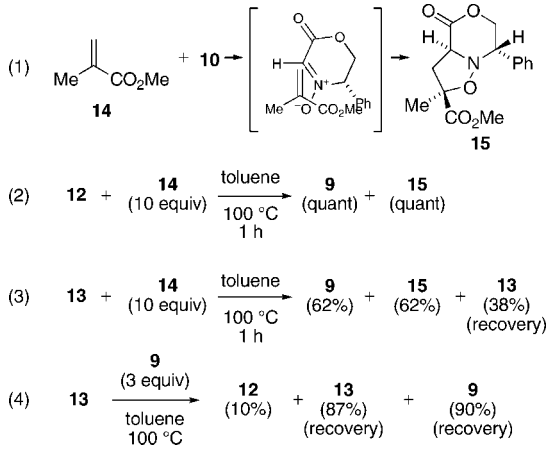
entry	solvent	temp (°C)	time (h)	**12**/**13**[c] (yield, %)[d]
1[a]	neat	−25	11	47:53 (40)
2[a]	neat	rt	11	45:55 (93)
3[a]	neat	60	11	22:78 (96)
4[a]	CH_3CN	rt	11	42:58 (46)
5[a]	THF	rt	11	50:50 (54)
6[b]	MeOH	rt	11	26:74 (55)
7[b]	hexane	rt	8	47:53 (quant)
8[b]	hexane	50	2.5	50:50 (quant)

[a] Nitrone **10** (1 equiv) and ethylideneindolinone **9** (1 equiv) were used. [b] Nitrone **10** (1 equiv) and ethylideneindolinone **9** (3 equiv) were used. [c] The ratios of products **12** and **13** were estimated from the ^{1}H NMR spectra. [d] The yields were estimated from the ^{1}H NMR spectra of the crude products.

should exhibit a higher ratio at lower temperature, these results imply that the present cycloaddition at high temperature might involve a thermodynamically controlled equilibium cycloreversion[9] of the cycloadducts **12** and **13** to the starting **9** and **10**. The effect of solvent polarity was next examined. Although reactions in polar solvents such as acetonitrile, tetrahydrofuran, and methanol did not go to completion at room temperature (entries 4−6), the use of hexane as a solvent, interestingly, accelerated the cycloaddition at the same temperature to give a ca. 1:1 mixture of **12** and **13** in quantitative yield (entries 7 and 8).[10] Taking into account the distribution of products as well as the solubility of the starting materials, neat conditions (entry 2) may be convenient for a large-scale reaction.

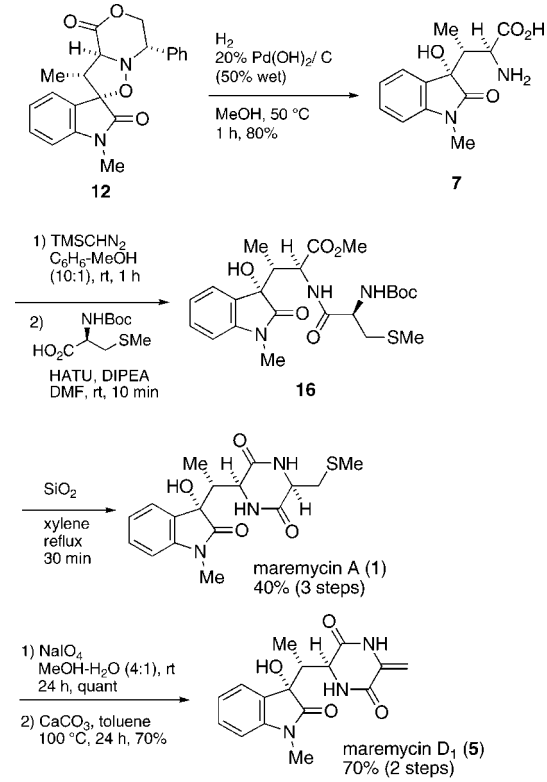
We next decided to investigate cycloreversion of the cycloadducts **12** and **13** (Scheme 3). It is known that methyl methacrylate (**14**) reacts with nitrone **10** to exclusively afford cycloadduct **15** in high yield (eq 1).[7d] Cycloadduct **12**, on heating with methacrylate **14** in toluene at 100 °C for 1 h, released 3-ethylideneindolin-2-one **9** and afforded cycloadduct **15** of methacrylate **14** in quantitative yield (eq 2). Similar treatment of cycloadduct **13** with **14** provided

Scheme 3. Cycloreversion of Cycloadducts **12** and **13**



3-ethylideneindolin-2-one **9** (62%) and cycloadduct **15** of methacrylate **14** (62%), along with recovery of **13** (38%) (eq 3). Formation of **15** from **12** or **13** would involve regeneration of nitrone **10** and indolinone **9**. Thus, heating **12** or **13** would cause cycloreversion to indolinone **9** and nitrone **10**, which, in turn, could undergo re-cycloaddition with methacrylate **14** to provide **15**. These facts (eqs 2 and 3) also suggest that cycloadduct **13** may be thermodynamically more stable than cycloadduct **12** because cycloadduct **13** exhibited lower cycloreversion reactivity on heating than did **12**.[11] Therefore, we considered the conversion of regioisomer **13** to the desired cycloadduct **12** via cycloreversion−re-cycloaddition (eq 4). When a mixture of regioisomer **13** and ethylideneindolinone **9** was heated in toluene, cycloreversion−re-cycloaddition occurred to give the desired cycloaddition product **12** in 10% yield accompanied with recovery of regioisomer **13** in 87% yield and ethylideneindolinone **9** (90%). Thus, the yield of the desired cycloadduct **12** can be improved by recycling this reaction.

Scheme 4. Synthesis of Maremycin A (**1**) and D_1 (**5**)



Cycloadduct **12** has the correct stereochemistry for maremycins A (**1**) and D_1 (**5**), and elaboration to **1** and **5** was readily achieved (Scheme 4). Thus, hydrogenolysis of cycloadduct **12** simultaneously caused reductive cleavage of the N−O bond and the benzylic position, followed by hydrolysis of the ester group to provide γ-hydroxy-α-amino acid **7**. Treatment of amino acid **7** with $TMSCHN_2$ followed by condensation with *N*-Boc-*S*-methyl-L-cysteine gave dipeptide **16**. When dipeptide **16** was heated with silica gel in

boiling xylene for 30 min, removal of Boc group and formation of the diketopiperazine ring occurred to afford maremycin A (**1**), mp 229.0−229.5 °C, $[\alpha]^{22}_{D}$ −110.2 (*c* 0.21, MeOH) [lit.[1] mp 229 °C, $[\alpha]^{20}_{D}$ −120.95 (*c* 0.21, MeOH)], whose ^{1}H and ^{13}C NMR spectra were identical with those reported.[1] The structure of maremycin A (**1**) has thus been established to be as depicted in Scheme 4. The methylthio group of **1** was oxidized to a methylsulfinyl group, and then thermal elimination afforded maremycin D_1 (**5**), mp 224.0−226.0 °C (decomp), $[\alpha]^{22}_{D}$ −40.8 (*c* 0.1, MeOH), whose ^{1}H and ^{13}C NMR spectra were identical with those reported.[2]

(9) For examples of cycloreversion of nitrone cycloadducts, see: (a) Schultz, A. G.; McMahon, W. G.; Kullnig, R. K. *J. Org. Chem.* **1987**, *52*, 3905–3909. (b) Burdisso, M.; Gamba, A.; Gandolfi, R.; Oberti, R. *Tetrahedron* **1988**, *44*, 3735–3748. (c) Giera, H.; Huisgen, R. *Liebigs Ann.* **1997**, 1685–1689. (d) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4900–4901. (e) Pisaneschi, F.; Cordero, F. M.; Brandi, A. *Synlett* **2003**, 1889–1891. (f) Garcia Ruano, J. L.; Fraile, A.; Martin Castro, A. M.; Martin, M. R. *J. Org. Chem.* **2005**, *70*, 8825–8834.

(10) Nitrone **10** and 3-ethylidene-1-methylindolin-2-one (**9**) are highly polar compounds whose oxygen atom may possess donating character, and hence they would not undergo stabilization in hexane, which has low polarity and low accepting ability. Since cycloreversion from cycloadducts **12** and **13** leading to nitrone **10** and indolinone **9** would become unfavorable in hexane, dominance of cycloadduct **13** may be suppressed, affording a 1:1 mixture of **12** and **13**.

(11) Computation (6-31G*) indicated that cycloadduct **13** is more stable by 1.47 kcal/mol than cycloadduct **12** (Supporting Information).

In conclusion, we have accomplished the first synthesis of maremycins A (**1**) and D_1 (**5**), featuring cycloaddition of cyclic nitrone **10** with (*E*)-3-ethylidene-1-methylindolin-2-one (**9**), and thereby conclusively determined the stereochemistries of the natural products **1** and **5**. In addition, **5** has been fully characterized for the first time. This short-step synthesis is expected to be suitable for obtaining large amounts of the natural products for biological screening.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **12**, **13**, **7**, **1**, and **5**; their ^{1}H NMR data; X-ray crystallography of **12**; 6-31G* calculations of **12** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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