aration of the substrate for this cyclization required two steps.

Treatment of benzoic acid 3 with oxaloyl chloride and addition of the reaction mixture to L-alaninamide gave crystalline diamide 4 (Scheme I). Selective reduction of the two amide groups in the presence of the nitro and chloro substituents was easily accomplished with $BH_3 \cdot SMe_2$ in refluxing THF.[6]

Cyclization to an intermediate tetrahydrobenzodiazepine was effected by heating crude diamine 5 in DMF containing solid K_2CO_3; regiospecific alkylation of the more nucleophilic amino group was accomplished by adding 3-methyl-2-butenyl bromide to the reaction mixture. This one-pot procedure afforded the penultimate product 6.

The nitro group of tetrahydrobenzodiazepine 6 was selectively hydrogenated in the presence of the side-chain olefin; after removal of the palladium catalyst by filtration, carbon disulfide was added and the resulting reaction mixture was heated. In the one-step procedure,[7] the nitro group was reduced and the resulting ortho diamine was capped with the thiocarbonyl group.

This four-step route, based on intramolecular nucleophilic aromatic substitution, provided the title compound 1a[8,9] in *18% overall yield* from commercially available 3. We anticipate that this efficient sequence will provide rapid access to a large number of novel TIBO analogues.

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Supplementary Material Available: Experimental procedures for the preparation of compounds 1, 4, 5, and 6 as well as spectra (^1H NMR, ^{13}C NMR and IR) for 1, 4, and 6 (13 pages). Ordering information is given on any current masthead page.

(6) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441.
(7) Ziv, J.; Knapp, S.; Rosen, J. D. *Synth. Commun.* **1988**, *18*, 973.

(8) Melting point 171-173 °C (lit.[1] mp 174.5 °C). $[\alpha]_D = +14.8°$ (c = 1, $CHCl_3$). Spectroscopic data for 1a: ^1H NMR ($CDCl_3$) δ 10.51 (bs, 1 H), 7.09 (m, 2 H), 6.89 (m, 1 H), 5.25 (t, J = 7.4 Hz, 1 H), 4.56 (dd, J = 3.2, 7.4 Hz, 1 H), 4.32 (d, J = 16.9 Hz, 1 H), 4.22 (dd, J = 8.8, 14.6 Hz, 1 H), 4.09 (d, J = 16.9 Hz, 1 H), 3.55 (m, 1 H), 3.16 (m, 2 H), 1.73 (s, 3 H), 1.44 (s, 3 H), 1.29 (d, J = 4.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.5, 135.7, 132.2, 130.2, 124.5, 123.3, 122.3, 121.6, 108.0, 56.0, 53.6, 52.4, 46.9, 25.9, 17.9, 17.8; IR (CCl_4) 3143, 3104, 1510, 1468, 1441, 1375, 1348, 1240, 1209, 1151 cm^{-1}; UV 308, 250, 225 nm; HRMS calcd for 287.1456, found 287.1467.

(9) The activity of TIBO R82150 in T4 lymphocytes (CEM cell line) was confirmed in the NIH screen. We are grateful to Drs. Robert Schultz and Mohamed Nasr for expediting in vitro testing of our compounds.

Radical Mediated Intramolecular [3-Atom + 2-Atom] Addition and the Synthesis of (±)-Rocaglamide: Model Studies

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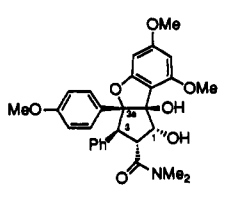
Summary: The cyclopenta[*b*]benzofuran ring system of the antileukemic natural product rocaglamide can be efficiently prepared by intramolecular [3 + 2] radical mediated addition. The stereochemical relationship that emerges between C(2) and C(3a) upon cyclization is identical with that seen in the natural product.

Rocaglamide (1) is the agent responsible for the antileukemic activity of extracts from the roots and stems of *Aglaia elliptifolia*.[1] Its structure, determined by single-crystal X-ray analysis, was reported in 1982,[1] and very recently its absolute stereochemistry was found to be as shown by total synthesis of the naturally occurring antipode.[2] The structural complexity of rocaglamide, coupled with its powerful biological activity,[1,3] combine to make it an attractive target for total synthesis.[4] Herein we report an efficient synthesis of the tricyclic cyclopenta[*b*]benzofuran framework of rocaglamide, as part of a study directed toward the total synthesis of this unique natural product.



1

Recently we have disclosed a radical mediated [3 + 2] addition methodology for the synthesis of substituted cyclopentanes utilizing functionalized vinylcyclopropanes and alkenes as reaction partners.[5] Substitution of an alkyne for the alkene allows for the efficient construction of cyclopentenes,[6] and we felt that an intramolecular variant of this latter reaction would be ideally suited for the construction of the rocaglamide skeleton.

To test such an hypothesis, we first synthesized the diastereomeric vinylcyclopropanes 6 in a straightforward six-step procedure (Scheme I).[7] Exposure of a benzene solution of diphenyl disulfide and either diastereomer of 6 (or a mixture of both diastereomers) to sunlamp irradiation affected smooth transformation to the cyclopenta[*b*]benzofuran system 7 in 94% yield. Notably, only

6 7

(1) King, M. L.; Chiang, C. C.; Ling, H. C.; Fujita, E.; Ochiai, M.; McPhail, A. T. *J. Chem. Soc., Chem. Commun.* **1982**, 1150.
(2) Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 9022.
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(4) For synthetic studies toward 1 see: (a) Taylor, R. J. K.; Davey, A. E. *J. Chem. Soc., Chem. Commun.* **1987**, 25. (b) Trost, B. M. *Pure. Appl. Chem.* **1988**, 1615. (c) Kraus, G. A.; Sy, J. O. *J. Org. Chem.* **1989**, *54*, 77.
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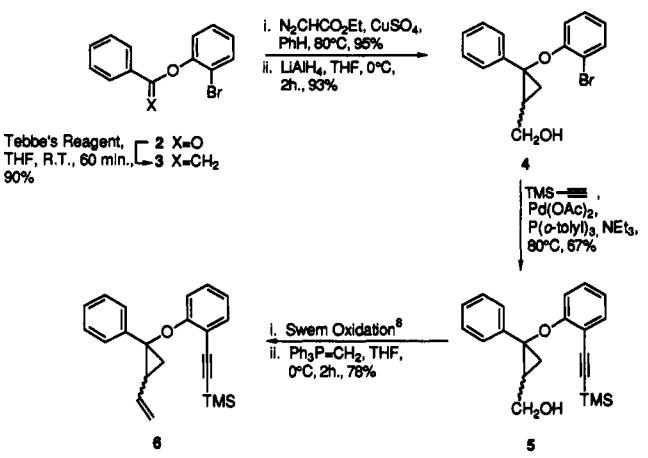
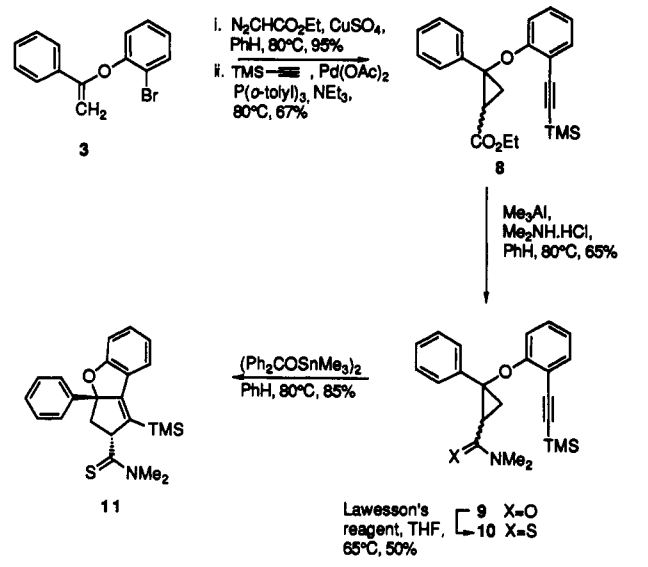
(6) Feldman, K. S.; Ruckle, R. E.; Romanelli, A. L. *Tetrahedron Lett.*, **1989**, *30*, 5845.

0022-3263/91/1956-4601$02.50/0

Scheme I



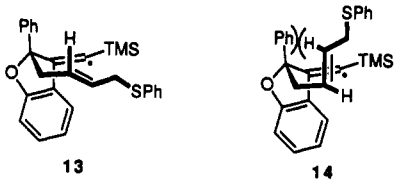
Scheme II



one diastereomer is formed from either diastereomeric vinylcyclopropane in this reaction. The relative stereochemistry of the pendant groups at C-2 and C-3a (rocaglamide numbering) is identical with that found in rocaglamide. This relative stereochemistry is assigned on the basis of the vicinal coupling observed between 2-H and the protons at C-3 (J = 9.3, 5.1 Hz). Molecular modeling calculations[9] predict a coupling of 11.5 and 3.3 Hz between these protons, while for the alternative cis diastereomer the expected coupling is 7.9 and 1.3 Hz.

Having demonstrated the efficacy of this intramolecular cyclization process for the construction of the rocaglamide skeleton, a more expeditious route to the natural product system, involving cyclization of the cyclopropyl thioamide **10**, was explored next. Treatment of the diastereomeric thioamides **10** (prepared as shown in Scheme II) with trimethyltin radical, generated from thermolysis of bis(trimethylstannyl)benzopinacolate,[10] gave the desired cyclized product **11** as the only isolated material.[11] As in the vinyl series, the relative stereochemistry of the product, assigned by comparison of the observed coupling between 2-H and 3-H (J = 9.4, 5.1 Hz) with that predicted from molecular modeling calculations,[9,12] is identical with that seen at C-2 and C-3a in rocaglamide.

In both the vinyl series **6** and the thioamide series **10**, the observed stereoselectivity upon cyclopentene formation can be rationalized by citing cyclization—to close the C-2/C-3 bond—through a transition state resembling the chairlike conformer **13** rather than the alternative boatlike construct **14**.



The intramolecular cyclization of both the vinylcyclopropanes **6** and the cyclopropyl thioamides **10**[13] represents a novel stereoselective approach to the synthesis of (±)-rocaglamide. Our continuing efforts in this area will be reported in due course.

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Supplementary Material Available: ^1H NMR, ^{13}C NMR, IR, MS, and spectroscopic data for **3**–**11** (4 pages). Ordering information is given on any current masthead page.

(7) All new compounds have been characterized by HRMS or microanalysis, and ^1H NMR, ^{13}C NMR, IR, MS. Diastereomers not readily separable by chromatography were characterized as mixtures. Spectroscopic data can be found in the Supplementary material.
(8) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.
(9) PCModel version 2.0, Serena Software.
(10) (a) Hillgärtner, H.; Neumann, W. P.; Schroeder, B. *Liebigs Ann. Chem.* **1975**, 586. (b) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631.
(11) Tin radical mediated ring opening of cyclopropyl ketones has been reported elsewhere: Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 589. For the ring opening of cyclopropyl thioketones, see: Adam, W.; Heil, M. *J. Am. Chem. Soc.* **1991**, *113*, 1730.
(12) Predicted coupling constants between 2-H and 3-H: trans isomer, J = 11.5, 6.0 Hz; cis isomer, J = 5.7, 1.2 Hz.
(13) Full details of the radical mediated reaction between cyclopropyl thioamides and alkenes or alkynes will be published elsewhere.