pH 6.3, and for which NOEs could not be observed previously. These are as follows: Lys-30 and Glu-31 at the end of the first calcium binding loop; Met-36 and Arg-37 in helix 2; Gly-40 and Gln-41 in the turn following helix 2; Leu-48 and Gln-49 in helix 3; Met-76 and Lys-77 in helix 4; Asp-80 and Ser-81 and Val-91 and Phe-92 in helix 5; Leu-105 and Arg-106, His-107 and Val-108, and Leu-112 and Gly-113 in helix 6; Val-121 and Asp-122 in helix 7; and Met-144 and Met-145 in helix 8. Of these pairs, the interaction between the NH protons of His-107 and Val-108 could not be determined because both ^{15}N shifts are also degenerate, and no NOE was observed between Asp-80 and Ser-81. (Note that the latter may be due to the fast amide exchange rates of both Asp-80 and Ser-81.) For the remaining 10 pairs, clear NOE interactions were observed. In addition, there are eight pairs of protons with chemical shift differences between 0.05 and 0.10 ppm for which NOEs are observed much more clearly than in the corresponding 3D NOESY-HMQC spectrum.

The 3D experiment described here provides important additional data with regard to determining the 3D structure of proteins. The method is applicable for ^{15}N- or ^{13}C-enriched proteins and furnishes information that is complementary to the popular heteronuclear edited NOESY 3D experiment.[3] If overlap occurs in the 3D NOESY-HMQC spectrum, this will generally be resolved in the 3D HMQC-(NOESY)-HMQC spectrum, and vice versa.

Acknowledgment. We thank Lewis Kay and Guang Zhu for the development of the linear prediction software used in this work and Marie Krinks for preparation of the calmodulin sample. This research was supported by the AIDS Directed Anti-Viral Program of the Office of the Director of the National Institutes of Health (A.B., G.M.C., and A.M.G.).

An Unusual Oxidative Cyclization. A Synthesis and Absolute Stereochemical Assignment of (-)-Rocaglamide

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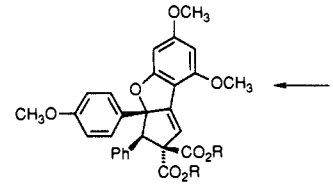
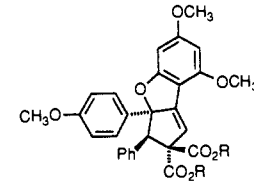
Rocaglamide (**1**), a novel natural product isolated from *Aglaia elliptifolia* Merr, has shown significant activity against P388 lymphocytic leukemia in CDF mice and human epidermoid carcinoma cells of the nasopharynx (in vitro).[1] While X-ray crystallography established the relative stereochemistry, the absolute stereochemistry remained to be defined.[1b] Furthermore, the high density of functionality makes the molecule a significant synthetic challenge.[2] Scheme I outlines our retrosynthetic analysis. In this paper, we record the first synthesis of rocaglamide, assignment of its absolute stereochemistry, and the development of a novel oxidative cyclization to create the dihydrobenzofuran ring (cf. **3** → **2**).

Pd-catalyzed cycloaddition of the substituted TMM precursor **5** and acceptor **6** (R = CH_3) [5 mol % $Pd(OAc)_2$, 30 mol % $(iC_3H_7O)_3P$, $PhCH_3$, reflux][3,4] gave the cycloadduct **4**[5] (X = CH_2, R = CH_3, *E*/*Z* mixture) in 92% yield. Ozonolysis [2:1 CH_3OH/CH_2Cl_2, 78%; $(CH_3)_2S$] was accompanied by equilibration to the *E* isomer **4** (X = O, R = CH_3) in 77-79% yield. The complex $BF_3{\cdot}CH_3OH$ (2 × 1.14 equiv) catalyzes (CH_2Cl_2, room temperature to reflux) the direct condensation of dimethyl phloroglucinol with the cyclopentanone **4** (X = O, R = CH_3) to give the adduct **3**[5] as a 2:1 mixture of olefin regioisomers (60% yield).

The oxidative cyclization of the regioisomeric olefin mixture **3** was envisioned to proceed via the allyl cation **7**. Charge neutralization at the center of highest positive charge should provide the required regioselectivity. Attack of the oxygen on the least hindered face of **7** anti to the phenyl group should provide the necessary diastereoselectivity (i.e., **8**), especially in an early-transition-state reaction. After much experimentation, DDQ[6]



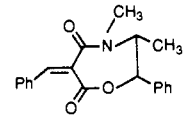
8 **7**



9

(THF, reflux) was found to give a 72-77% yield of a single crystalline cyclized product. Spectroscopic data clearly established the regiochemistry as predicted. Surprisingly, the stereochemistry proved to be that represented in **9**[5] (attack from the more hindered face!) as established by X-ray crystallography. Apparently the unusual compactness of the highly substituted molecule makes the developing aryl-aryl interaction dominate, a most unusual result, considering that the reaction should follow an early transition state.

Thus, an asymmetric synthesis of rocaglamide via our route must take into account an ultimate inversion of the stereochemistry of the phenyl group. Since the absolute stereochemistry was not known, we chose to embark upon a synthesis of the enantiomer depicted in formula **1**. Cycloaddition of the oxazepinedione **10**[7] as described above (85% yield) followed by hydrolysis (NaOH, C_2H_5OH, reflux), esterification (CH_2N_2, C_2H_5OAc, room temperature), and ozonolysis (vide supra) gave the optically pure adduct **11**,[5] $[\alpha]_D = +27.8°$ (c = 2.1, $CHCl_3$). Condensation with



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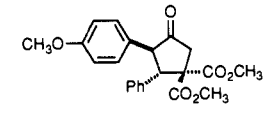

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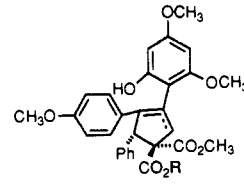

12

a) R = CH_3
b) R = CH_2Ph

(1) (a) McPhail, A. T.; King, M. L.; Chiang, C. C.; Ling, H. C.; Fujita, E.; Ochiai, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1150. King, M. L.; Ling, C. H.; Wang, C. B.; Leu, S. C. *Med. Sci.* **1975**, *1*, 11. (b) Private communication from Professor McPhail.

(2) For earlier synthetic efforts, see: (a) Taylor, R. J. K.; Davey, A. E. *J. Chem. Soc., Chem. Commun.* **1987**, 25. (b) Kraus, G. A.; Sy, J. O. *J. Org. Chem.* **1989**, *54*, 77.

(3) For a review, see: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

(4) Cf.: Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668.

(5) This compound has been characterized spectroscopically and its elemental composition established by combustion analysis and/or high-resolution mass spectroscopy.

(6) Cf.: Gardilla, G.; Cricehio, R.; Merlini, L. *Tetrahedron Lett.* **1969**, 907.

(7) Trost, B. M.; Yang, B.; Miller, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 6482.

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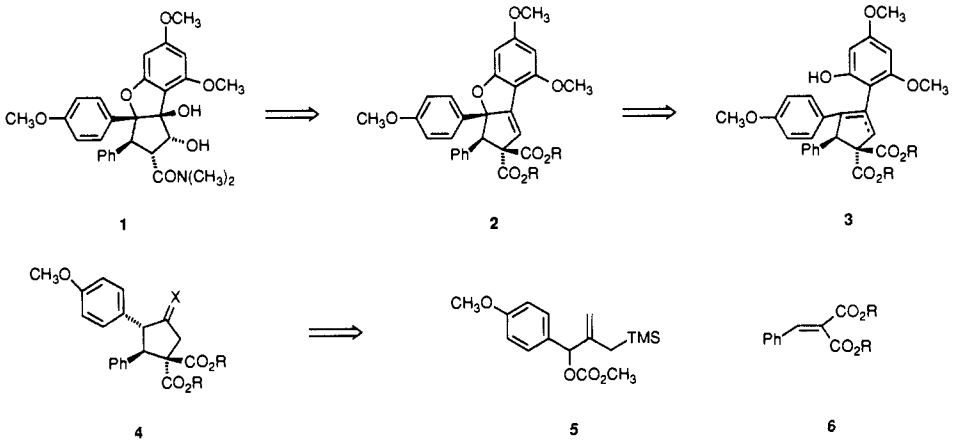
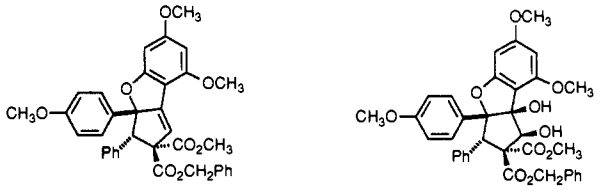
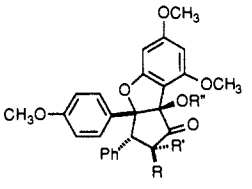
Scheme I. Retrosynthetic Analysis of (−)-Rocaglamide (**1**)



dimethyl phloroglucinol as above gave **12a**. Work in the racemic series revealed that subsequent decarbomethoxylation was difficult, whereas decarbobenzyloxylation proceeded cleanly. Transesterification[8] with benzyl alcohol [$Ti(OCH_2Ph)_4$, $PhCH_2OH$, 100 °C, 78%] afforded a single product in which only one ester exchanged. Steric considerations led us to tentatively assign the structure as **12b**.[5] Oxidative cyclization as before (75% yield) gave the complete nucleus **13**, $[\alpha]_D$ +89.9° (c = 1.76, $CHCl_3$). Catalytic hydroxylation[9] to diol (**14**, $[\alpha]_D$ −67.9° (c = 1.06, $CHCl_3$) proved to be erratic (45–83%) until we added 1 equiv of DABCO[10] to the usual conditions [4 mol % OsO_4, 2 equiv of NMO, 5:1 THF/H_2O, room temperature, 73%]. Moffatt–

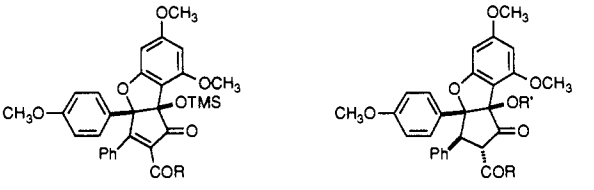




a) R = CO_2CH_3, R' = CO_2CH_2Ph, R'' = H
b) R = CO_2CH_3, R' = CO_2CH_2Ph, R'' = TMS
c) R = CO_2CH_3, R' = H, R'' = TMS

Doering oxidation[11] [1.1 equiv of $C_5H_5N{\cdot}SO_3$, DMSO, $(C_2H_5)_3N$, room temperature] followed immediately by silylation [$TMSOSO_2CF_3$, $(i\text{-}C_3H_7)_2NC_2H_5$, PhH, room temperature] and decarbobenzyloxylation [10% Pd/C, C_2H_5OH, 1 atm of H_2] gave the keto ester **15c**[5,12] (60% overall) as a 3:1 keto/enol mixture.

Adjustment of the stereochemistry envisioned proceeding through the enone **16** since it appears that the steric hindrance offered by the *p*-anisyl group precludes the normally anticipated preferences for approach of reagents to the convex face. Attempts



a) R = OCH_3
b) R = $N(CH_3)_2$

a) R = OCH_3, R' = TMS
b) R = $N(CH_3)_2$, R' = TMS

to introduce the double bond into **15c** by selenylation–dehydroselenylation[13] failed, whereas sulfenylation [NaH, PhSCl, THF, room temperature] followed by dehydrosulfenylation [MCPBA, $NaHCO_3$, CH_2Cl_2, −20 °C][14] gave a 72% yield of the enone **16a**, $[\alpha]_D$ = −125.1° (c = 1.22, $CHCl_3$), in addition to 8% of the desilylated enone. Catalytic hydrogenation [PtO_2, H_2 (1 atm), C_2H_5OH] completed creation of the correct diastereomer **17a**. Since attempts to effect amide formation at this stage or later failed, we examined amide formation with an earlier intermediate. Conveniently, the enone **16a** smoothly undergoes amidation under Weinreb's conditions[15] [$(CH_3)_2NH_2Cl$, $(CH_3)_3Al$, PhH, 45 °C] to give a 70–79% yield of the amide **17b**,[5] $[\alpha]_D$ = −246.8° (c = 1.41, $CHCl_3$). Reduction as before proved troublesome but again generated only a single diastereomer. Use of Pearlman's catalyst [20% $Pd(OH)_2/C$, H_2 (1 atm), C_2H_5OH, room temperature] proved completely reproducible but generated a 2–3:1 diastereomeric mixture favoring **17b**. The crude amide was directly desilylated [KF, CH_3OH, 40 °C] and diastereoselectively reduced from the β-face by templating the reducing agent with the neighboring hydroxyl group[16] [$(CH_3)_4NB(OAc)_3H$, CH_3CN, HOAc, room temperature] to give (−)-rocaglamide in 50% overall yield for the three steps. Chromatographic, spectroscopic, and physical properties are identical with those of an authentic sample.[17]

This synthesis establishes the absolute configuration. The identity of the sign of optical rotation of our synthetic sample, $[\alpha]_D$ −88.8° (c = 1.03, $CHCl_3$), whose absolute configuration corresponds to that depicted in **1**, with that of authentic rocaglamide establishes the identity of absolute stereochemistry. The

(8) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenburger, P.; Weidmann, R.; Zuger, M. *Synthesis* **1982**, 138.
(9) Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(10) Cf.: Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766. However, for rate retardation of amines, also see: Jacobson, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737.
(11) Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505. Many oxidants led to complex mixtures or carbon–carbon bond cleavage.
(12) Kraus reports **15** (R = CO_2CH_3, R' = R'' = H), which we also prepared. Our data is in good accord with that reported by Kraus except that we observed the keto form to dominate in contrast to the Kraus report.
(13) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. Renga, J. M.; Reich, H. J. *Org. Synth.* **1980**, *59*, 58.
(14) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. Harpp, D. A.; Friedlander, B. T.; Smith, R. A. *Synthesis* **1979**, 181.
(15) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(16) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. Also see: Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273.
(17) Mp 118 °C dec. We observe identical behavior for an authentic sample although mp 118–9° has been recorded.[1]

unusual diastereoselectivity of the oxidative cyclization and catalytic hydrogenation clearly reveals the steric congestion associated with this novel system. Important future goals include correlating the importance of such unusual conformational effects with biological activity and defining the scope and mechanism of the novel oxidative cyclization.[18]

Acknowledgment. We thank the General Medical Sciences Institute of the National Institutes of Health for their continuing generous support of our programs. P.D.G. and M.G.S. thank the NIH for postdoctoral fellowships. We are especially grateful to Mr. Chris Myers for the X-ray structural determination. We thank Dr. Pichael Wiriyachitra of the Faculty of Pharmacy, Chiang Mai University, for an authentic sample of (-)-rocaglamide. Mass spectra were gratefully provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: Characterization data for **1**, **3**, **4**, **9**, **11**, **12a,b**, **13**, **14**, **15c**, and **16a,b** (3 pages). Ordering information is given on any current masthead page.

(18) The initial exploratory work of M.G.S. was performed at the Department of Chemistry, University of Wisconsin—Madison.

Diazirinyl Anion: A Cyclic 4π-Electron System

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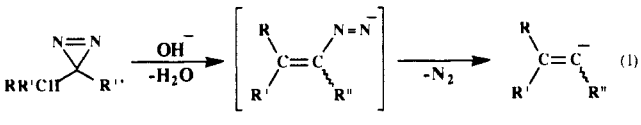
3*H*-Diazirines (**1**)[1] are cyclic isomers of diazo compounds and are characterized by a three-membered ring with a nitrogen–nitrogen double bond. This ring system was originally proposed in the literature about 100 years ago in order to explain the structure of diazomethane and ethyl diazoacetate.[2] However, it was not until 1960/1961 that Paulsen, and then Schmitz and Ohme, prepared the first authentic derivatives of **1**.[3] They were found, somewhat surprisingly, to be remarkably stable thermally and chemically.[4] Hundreds of diazirines have subsequently been prepared, and they have become the subject of increasing attention.[5]

We have recently reported that diazirines are practical reagents for the gas-phase preparation of vinyl anions (eq 1).[6] The mechanism for this reaction presumably involves an elimination pathway leading to a diazenyl anion intermediate (**2**), which rapidly evolves nitrogen to afford the observed product ions. This



1 **2** **3**

procedure is useful because vinyl anions are exceedingly reactive species that have proven to be difficult to generate by other means.[7]

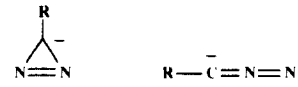
(1) Hereafter referred to simply as diazirine(s).
(2) (a) von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1888. (b) Curtius, T. *J. Prakt. Chem.* **1889**, *39*, 107.
(3) (a) Paulsen, S. R. *Angew. Chem.* **1960**, *72*, 781. (b) Schmitz, E.; Ohme, R. *Angew. Chem.* **1961**, *73*, 115.
(4) **CAUTION**: While many diazirines are thermally more stable than their corresponding diazo isomers, they must still be treated with great caution. Explosive decompositions have been reported.
(5) For example, see: *Chemistry of Diazirines*; Liu, M. T., Ed.; CRC Press: Boca Raton, FL, 1987; Vols. 1 and 2 and references therein.
(6) Anderson, K. K.; Kass, S. R. *Tetrahedron Lett.* **1989**, *30*, 3045.
(7) An alternative method involves collision-induced dissociation. For details, see: (a) Froelicher, S. W.; Freiser, B. S.; Squires, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 2853. (b) Graul, S. T.; Squires, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 607. (c) Graul, S. T.; Squires, R. R. *J. Am. Chem. Soc.* **1989**, *111*, 892 and references therein.

Table I. Summary of Results of Proton Transfer from Reference Acids and Bases to **6** and **6a**

ref compd	ΔH_{acid}[a]	ΔG_{acid}	proton transfer[b] ref acid	proton transfer[b] conjugate base
NH_3	403.7	396.0	-	+
$MeNH_2$	403.2	395.8	-	+
$EtNH_2$	399.4	391.7	+	-
Me_2NH	396.3	389.1	+	-
H_2O	390.8	384.1	+	-
MeOH	381.2	375.0	+	-

[a] Acidities are in kcal mol^{-1} and come from ref 9. [b] A "+" indicates the occurrence and a "-" denotes the absence of proton transfer.

When monosubstituted diazirines (R″ = H) are reacted, not only is the expected 1-alkenyl anion (**3**) produced, but a small amount ($\leq\sim$10%) of a deprotonated ion (P - 1) is also formed. Two reasonable alternatives for the structure of this product are a diazirinyl anion (**4**) or a diazo anion (**5**). The former species are



4 **5**

cyclic 4π-electron systems, antiaromatic at least in the Hückel sense,[8] and theoretically interesting, but have not been reported previously. In contrast, the latter ions, which could arise from the cleavage of a carbon–nitrogen bond in **4**, are well-known both in solution and in the gas phase and undoubtedly are favored thermodynamically. The identity of the P - 1 ions, however, was not ascertained because they were not formed in sufficient quantities to characterize them. In this communication, we now report that *tert*-butyldiazirine and the parent compound, neither of which can undergo an elimination reaction due to the absence of a β-hydrogen, both lead to the exclusive formation of a P - 1 ion. The reactivity of the resulting species is quite similar, and the structure, reactivity, and proton affinity of the parent system are described herein.

Diazirine (**6**) is not very acidic in the gas phase. It reacts with NH_2^- and $MeNH^-$, in our flowing afterglow apparatus, to afford a P - 1 ion (*m/z* 41), but is inert to weaker bases such as OH^-, Me_2N^-, and even $EtNH^-$ (see Table I). This data reflects either the thermodynamic acidity of **6** or the presence of a kinetic barrier to deprotonation. By examining the reverse process and noting that the P - 1 ion is a strong base (it deprotonates MeOH, H_2O, Me_2NH, and $EtNH_2$), the latter possibility can be ruled out. Consequently, we assign ΔH_{acid} (**6**) = 401 ± 3 kcal mol^{-1} and ΔG_{acid} (**6**) = 394 ± 3 kcal mol^{-1}. Diazomethane (**7**) is almost 30 kcal mol^{-1} more acidic than diazirine (ΔH_{acid} (**7**) = 373 ± 3 kcal mol^{-1} and ΔG_{acid} (**7**) = 365 ± 3 kcal mol^{-1}),[10] and thus the structure of the *m/z* 41 ion cannot be that of the diazomethyl anion (**7a**). On the basis of these results, the reactivity of the P - 1 ion, consideration of all the other isomers,[11] and molecular

(8) Cyclization to the diazirinyl anion leads to a destabilization of 0.48β if one uses the parameters for nitrogen ($\alpha_N = \alpha_C + 0.38\beta_{CC}$; $\beta_{CN} = 0.70\beta_{CC}$; $\beta_{NN} = 1.27\beta_{CC}$) given by Hess et al.: Hess, B. A.; Schaad, L. J.; Holyoke, C. W., Jr. *Tetrahedron* **1975**, *31*, 295.
(9) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1.
(10) DePuy, C. H.; Van Doren, J. M.; Gronert, S.; Kass, S. R.; Motell, E. L.; Ellison, G. B.; Bierbaum, V. M. *J. Org. Chem.* **1989**, *54*, 1846.
(11) Cyanamide (NH_2CN) is quite acidic (ΔH_{acid} = 350 ± 3 kcal mol^{-1}), and given the difference between ΔH_{acid} (CH_3CN) and ΔH_{acid} (CH_3NC) (-1.8 kcal mol^{-1}),[12] it seems reasonable to anticipate that isocyanamide (NH_2NC) will also be more acidic than **6**. A reasonable model for the upper limit of the acidity of 2*H*-diazirine ($C\overline{H{=}NNH}$) is 3,3-dimethylcyclopropene (ΔH_{acid} = 381 ± 3 kcal mol^{-1}). Thus, all three compounds appear to be more acidic than **6**, and an unlikely hydrogen rearrangement from carbon to nitrogen need not be proposed. In addition, the observed reactivity of the P - 1 ion would be difficult to rationalize in terms of the conjugate bases of these three compounds.
(12) Filley, J.; DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1987**, *109*, 5992.
(13) Kroeker, R. L.; Bachrach, S. M.; Kass, S. R. Manuscript submitted for publication.

0002-7863/90/1512-9024$02.50/0