Thus, it appeared that data from AMPAC might be useful in refining our newly developed parameters. We compared dihedral driver data from AMPAC and MODEL for a series of simple substituted β-lactams, using our new MODEL β-lactam parameters. Only in the case of the sulfone substituent were there any major discrepancies. It is our belief that the AMPAC data was not to be completely trusted in the sulfone case, as it is known that hypervalent sulfur compounds are not well described in the AM1 Hamiltonian.[14,15]

We experimented with numerous parameter sets in an attempt to match the AMPAC data, and found that any MODEL parameter set that would reproduce the AMPAC data gave poor structural data for the sulfone β-lactams. In the course of this effort, however, we did derive an additional parameter set that gave good structural data unrelated to the AMPAC information. These additional parameters are completely different from those derived from X-ray data, yet they give as good or better structural results. It is unclear at this time which of the new parameter sets is best for sulfone β-lactams. The limited number of structures does not as yet allow for this distinction. With more data, one set may well emerge as superior.

(13) Dihedral driver calculations involve using AMPAC to locate the global minimum. All structural features are then held constant at the calculated minimum-energy values except for the relevant dihedral angles. These are rotated through 360° with 10° increments, giving the torsional barrier to rotation. This approximates the rigid rotor option available in MODEL. We compared the data from these two sources and found remarkable agreement for a variety of systems including β-lactams, formamides, and alkanes. It is likely that AMPAC data can be used to derive MODEL parameters by adjusting these parameters to give a MODEL torsional curve matching the AMPAC curve.

(14) Dewar, M. J. S.; McKee, M. L. *J. Comp. Chem.* **1983**, *4*, 84.

(15) Stewart, J. J. P. *J. Comp. Chem.* **1988**, *66*, 2715.

Conclusions

The need for easily accessed, useful structural data prompted us to use molecular mechanics calculations. Recognition that the original parameters were poor led to our development of these new parameters. We believe the new parameters are useful in giving accurate structural data for β-lactams. Although force field calculations have certain weaknesses, the ease of the development of new parameters is a major asset and adds greatly to the utility of these techniques.

Supplementary Material Available: Tables containing MM-2 atom types, X-ray and MODEL data for selected β-lactams, and X-ray and AMPAC derived parameters for MM-2 calculations on β-lactams (7 pages). Ordering information is given on any current masthead page.

Samarium(II) Iodide Mediated Carbocycles from Carbohydrates: Application to the Synthesis of the C Ring of Anguidine

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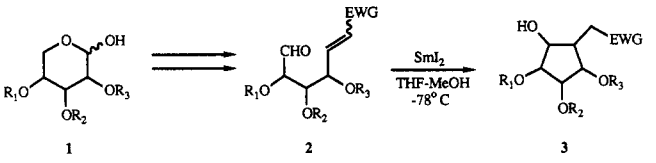
Summary: The enantioselective synthesis of the C ring of anguidine in protected form has been achieved from the known protected (L)-arabinose lactol **7**. A key transformation in this route involved the diastereoselective samarium diiodide mediated cyclization of carbohydrate template **11** to the highly oxygenated carbocycle **12**. The stereochemistry of this cyclization was confirmed by a combination of chemical transformations and nuclear Overhauser effect studies.

Sir: Recently, there has been considerable interest in the transformation of carbohydrates to carbocycles.[1] Most current technology involves a free-radical approach in which tributyltin hydride mediates a well-known 5-hexenyl-type of radical cyclization from a bromide, iodide, or thiocarbonyl imidazole precursor.[2] We have examined a different methodology which also directly addresses this synthetic problem; however, it differs in that it utilizes the one-electron reducing agent, samarium diiodide,[3] to couple

Scheme I



two sp^2-hybridized carbon centers in a modified carbohydrate template to construct a polyoxygenated cyclopentane ring, shown in Scheme I.[4] In this paper, we detail the first application of this methodology to an efficient enantioselective construction of the highly oxygenated C ring of anguidine.

(1) (a) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609. (b) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. (c) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546. (d) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (e) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759. (f) Vite, G. D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2268. (g) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102. (h) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522.

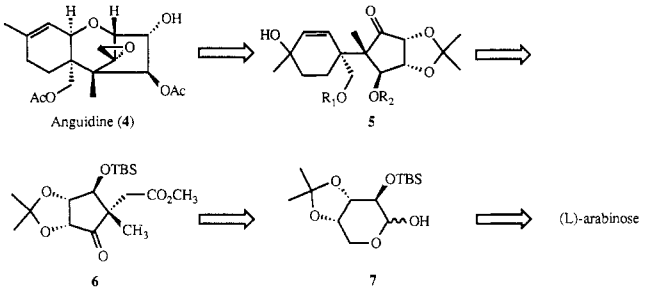
(2) For a review of these processes see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986. (b) Curran, D. P. *Synthesis* **1988**, *417*, 489. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Neumann, W. P. *Synthesis* **1987**, 665.

(3) For a reviews on samarium diiodide-mediated reactions, see: (a) Natale, N. R. *Org. Prep. Proced. Int.* **1983**, *15*, 387. (b) Kagan, H. B. *Fundamental and Technological Aspects of Organo-f-Element Chemistry*; Marks, T. J., Fragara, I. L., Eds.; NATO ASI: Dordrecht, 1985; pp 49–76. For recent applications of samarium diiodide in synthesis, see: (c) Molander, G. A.; Etter, J. B. *Tetrahedron Lett.* **1984**, 3281. (d) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778. (e) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (f) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132. (g) Molander, G. A.; Etter, J. B. *Synth. Commun.* **1987**, *17*, 901. (h) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556. (i) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064 and references therein. (j) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920. (k) Fukuzawa S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669, and references therein. (l) Molander, G. A.; Kenny, C. *Tetrahedron Lett.* **1987**, 4367.

(4) (a) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463. (b) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, 1063.

0022-3263/89/1954-5841$01.50/0

Scheme II



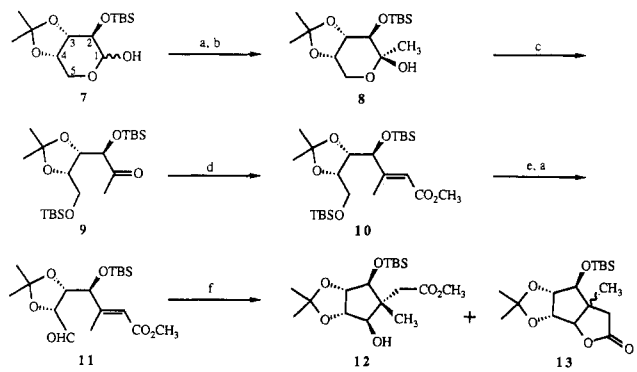
Anguidine is a member of the trichothecene family of sesquiterpenes which collectively represent a formidable challenge to synthetic organic chemists.[5] These compounds are a group of fungal metabolites produced by various species of *Fungi imperfecti* which exhibit a wide range of antifungal, antibacterial, antiviral, and other biological activities.[6] An important anticancer and cytopathological agent, the trichothecene anguidine, is also a structurally interesting synthetic target; however, only a single effort by Brooks and co-workers[7] involved the successful utilization of an enantioselective approach.

There were several considerations in our assessment of the C ring in anguidine which had to be dealt with in the overall antithetic analysis of this molecule, shown in Scheme II. First, because the structure–activity relationships of anguidine are not well understood, the route should be flexible enough with regard to protecting groups and other manipulations to prepare intermediates in the latter stages of the synthesis for biological testing. Secondly, the approach should be versatile enough to permit the synthesis of other members of the trichothecene family. Thirdly, the synthesis had to be simpler and/or more efficient than the previous effort.[7]

Thus, cyclopentanone **6**, which contains all of the necessary oxygenated functionality and stereochemistry for the assembly of anguidine, represents a protected version of the C ring for these studies. The sensitive spiroepoxide functionality in the C ring can be easily constructed at a later stage in the synthesis from the precursor ketone moiety, and this has been demonstrated in several previous racemic routes to trichothecenes.[5] The key observation in our plan was the recognition that **6** could arise from the protected carbohydrate lactol **7** by the samarium diiodide reductive process outlined in Scheme I.[4] It is noteworthy that the carbohydrate template must be deoxygenated and a new quaternary sp^3 carbon center must be established in this sequence. This unique approach to the synthesis leads to considerable retrosynthetic simplification, which is reflected in the subsequent enantioselective construction of this densely oxygenated cyclopentane system.

Our synthesis, shown in Scheme III, begins with the known lactol **7**,[8,9] which is readily available in high yield

Scheme III[a]



[a] (a) PDC, CH_2Cl_2, 3-Å molecular sieves, HOAc; (b) MeLi, THF, −78 °C; (c) *tert*-butyldimethylsilyl chloride, DMF, imidazole; (d) $(EtO)_2POCH_2CO_2CH_3$, NaH, THF; (e) Amberlite-H^+, MeOH; (f) SmI_2, THF, MeOH, −78 °C.

from the inexpensive carbohydrate (L)-(+)-arabinose. This compound was oxidized with pyridinium dichromate and treated with methyllithium at low temperature to afford hemiketal **8**[10] in 79% and 61% yields, respectively. The lactone and the hemiketal from this process were both highly crystalline materials, and only a single diastereomer with the stereochemistry depicted for **8** was isolated.[11] Although a mixture was anticipated at this step, the endo stereochemistry probably reflects the steric requirements for the approach of the methyl nucleophile and avoidance of the adjacent bulky *tert*-butyldimethylsiloxy functionality.[12]

The single diastereomer obtained for **8** was actually inconsequential because a subsequent treatment with *tert*-butyldimethylsilyl chloride, under standard conditions, produced the acyclic ketone **9** in 97% yield. Next, an Emmons variation of the Wittig reaction with the sodium salt of methyl diethylphosphonodiacetate rendered the exclusive trans geometric isomer for the α,β-unsaturated ester **10** in 90% yield. This was confirmed by difference NOE studies in which irradiation of the sole olefin proton caused a 6.6% enhancement of the C_2 (arabinose numbering) proton. The cis isomer could not be observed by either ^1H NMR or chromatographic methods. The removal of the sterically most accessible *tert*-butyldimethylsilyl protecting group under acidic conditions liberated the primary hydroxyl functional group in 60% yield. A number of other deprotection methods, unfortunately, resulted in partial or complete decomposition of **10**. An uneventful chromate-based oxidation then led to the preparation of the modified carbohydrate template **11** in 96% yield.

The trans geometric isomer for **11** was a desirable prerequisite for anticipated success in the SmI_2 reductive cyclization in this reaction sequence. With other carbohydrate templates we have observed a correlation with the starting olefin geometry and the product diastereoselectivity, where we expected the anti diastereomer to prevail in the subsequent samarium diiodide reduction from the trans olefin.[4]

(5) For reviews on the chemistry of the trichothecenes, see: (a) Tamm, C.; Breitenstein, W. *The Biosynthesis of Mycotoxins*; Steyn, P. S., Ed.; Academic Press: New York, 1980. (b) Tamm, C. *Fortschr. Chem. Org. Naturst*, **1974**, *31*, 63. (c) Doyle, T. W.; Bradner, W. T. *Anticancer Agents Based on Natural Product Models*, Academic Press: New York, 1980. (d) McDougal, P. G.; Schmuff, N. R. *Prog. Chem. Org. Nat. Prod.* **1985**, *47*, 153, and references therein.

(6) Bamberg, J. R. *Proc. Mol. Subcell.* **1983**, *8*, 41.

(7) (a) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, *J. Am. Chem. Soc.* **1983**, *105*, 4472. (b) Brooks, D. W., Grothaus, P. G.; Palmer, J. T. *Tetrahedron Lett.* **1982**, 4187.

(8) All new compounds exhibit ^1H NMR, ^{13}C NMR, mass spectrum, IR, and combustion analysis, or accurate mass spectrum consistent with the structure shown.

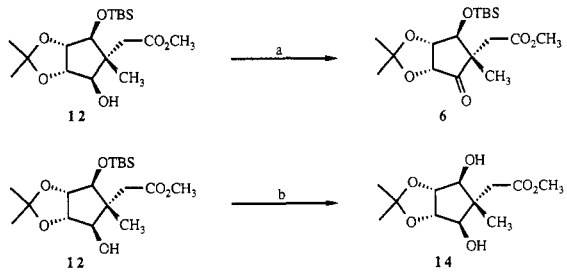
(9) Schorkhuber, W.; Zbiral, E. *Justus Liebigs Ann. Chem.* **1980**, 1455.

(10) The other compound identified in this reaction was the dimethylated acyclic product which was observed in <10% yield.

(11) The stereochemistry for **8** was confirmed by difference NOE studies by irradiation of the methyl substituent which showed a 6.0% enhancement in the C_2 (arabinose numbering) proton.

(12) A quite different thermodynamic argument for the stereochemistry of **8** arises from the anomeric effect. It is possible that the hemiketal stereochemistry with the endo-disposed methyl is the thermodynamically most stable product and a result of equilibration through the acyclic keto alcohol form.

Scheme IV[a]



[a] (a) PDC, CH_2Cl_2, 3-Å sieves, HOAc; (b) *n*-Bu_4NF, THF, 23 °C.

It should be noted that a more direct means of constructing carbohydrate template **11** can be envisioned as arising from a direct Wittig with hemiketal **8**, which would apparently avoid the protection–deprotection sequence realized above. However, in our previous experience with Wittig reactions of arabinose lactols[4] with stabilized ylides, we have only observed the undesired cis isomer as the major product. Similar results with furanose lactols have been observed by Wilcox and co-workers.[13] It appears that the C_5 hydroxyl functionality in the acyclic form of the lactol plays a role in the formation or decomposition of the oxaphosphatane and leads to a predominance of the cis isomer. Blocking the C_5 hydroxyl functionality as its *tert*-butyldimethylsilyl ether and "locking" the hemiketal in its acyclic ketone form insures the trans product will predominate in the Emmons Wittig reaction.[13]

Thus, treatment of **11** with samarium diiodide in tetrahydrofuran at −78 °C in the presence of methanol as a proton donor produced the highly oxygenated cyclopentane **12** and a minor lactone product **13** in a ca. 5:1 ratio, respectively, as shown in Scheme III. The major product could be easily isolated by flash chromatography in 65% yield. A final oxidation of the sole ring hydroxyl funtionality to ketone **6** in 81% yield completed the synthesis of the protected C ring of anguidine, as shown in Scheme IV.

The stereochemistry of **12** was confirmed by deprotection of the *tert*-butyldimethylsiloxyl moiety by treatment with fluoride ion. A plane of symmetry was clearly apparent in *syn*-diol **14** as was evidenced by the simple ^1H NMR and the 10-line ^{13}C NMR spectra. Additional confirmation of the stereochemistry of this cyclization came from difference NOE experiments. Irradiation of the methylene protons on the ester appendage produced a 9.8% enhancement of the two equivalent β-disposed protons on the hydroxy-bearing ring carbons. Thus, a combination of chemical and spectroscopic methods unequivocally confirmed the stereochemistry of this polyoxygenated ring.

In conclusion, the enantioselective synthesis of the C ring of anguidine has been accomplished in eight steps from the known (L)-arabinose lactol **7**. The key transformation involved the one-electron reductant samarium diiodide in the transformation of a carbohydrate to a carbocycle. In this reaction, the stereoselective cyclization of **11**, which contains an aldehyde tethered to an activated alkene, produced the polyoxygenated cyclopentane **12**, a crucial intermediate in the synthesis. Additional efforts in the samarium diiodide mediated conversion of carbohydrates to carbocycles and their use in synthesis will be reported in due course.

Acknowledgment. Support for this work from the American Cancer Society (Grant No. IN47495), the Division of Sponsored Research, and the Department of Chemistry at the University of Florida is gratefully acknowledged.

(13) Webb, T. H.; Thomasco, L. M.; Schlachter, S. T.; Gaudino, J. J.; Wilcox C. S. *Tetrahedron Lett.* **1988**, 6823.

The Chemistry of Vicinal Tricarbonyls. A Total Synthesis of (±)-3-Demethoxyerythratidinone

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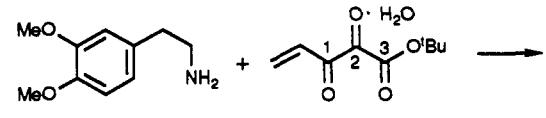
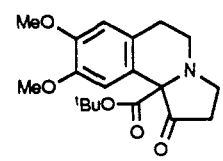
Summary: The tricyclic pyrrolidone carboxylate **3** formed from the reaction of 2-(3,4-dimethoxyphenyl)ethylamine (**1**) with the vinyl tricarbonyl reagent **2** has been converted to the erythrina alkaloid (±)-3-demethoxyerythratidinone (**12**).

Sir: In an earlier report on the chemistry of tricarbonyl systems we described the reaction of 2-(3,4-dimethoxyphenyl)ethylamine (**1**) with the vinyl tricarbonyl ester **2** followed by treatment with a Lewis acid ($POCl_3$) to yield the tricyclic product **3**.[1] The ready formation of **3** is a consequence of the enhanced reactivity of the central carbonyl at C-2 in **2** which, together with the adjacent α,β-unsaturated carbonyl grouping, provides a trielectrophilic receptor for the donor sites in **1**. This reaction is of special interest in that the two carbonyl groups at C-1 and C-3 in **2**, which play an activating role in the reaction of **1** with **2**, remain favorably disposed for further elaboration of the tricyclic product **3** to the tetracyclic system found in the erythrina family of alkaloids.



1 **2**



3

We now describe the use of compound **3** for the formation of (±)-3-demethoxyerythratidinone (**12**). This alkaloid, first isolated from *Erythrina lithosperma* by Barton,[2,3] has been synthesized in a number of recent in-

(1) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371.

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