Armed/Disarmed Effects and Adamantyl Expansion of Some Caged Tricyclic Acetals *en Route* to Tetrodotoxin[1,2]

Christopher S. Burgey,[3a] Roland Vollerthun,[3b] and Bert Fraser-Reid*

Paul M. Gross Chemical Laboratory, Duke University, Department of Chemistry, Durham, North Carolina 27708

Received September 25, 1995[⊗]

Transformation of the previously prepared tricyclic ketone **4** into an advanced intermediate, **2a**, of the Kishi−Goto synthesis of tetrodotoxin requires, among other things, cleavage of the internal acetal. In our attempts to carry this out, we were confronted by two major obstacles, one resulting from armed/disarmed effects encountered during acid-catalyzed acetolyses. Thus ester protecting groups proximal to the acetal moiety inhibited cleavage, e.g., **4** → **8a** and **7** → **8b**. Although the corresponding ether analogs **9a** and **9b** did undergo acetolysis, the products obtained, **10a** and **10b**, respectively, revealed the second obstacle, namely the proclivity of the caged systems to undergo adamantyl expansion. The latter result was found to depend upon the presence of properly positioned nucleophilic substituents. Thus **11b** underwent adamantyl expansion to **12b** but its C7 epimer **15** experienced facile cleavage to bicyclic product **16**. As an alternative to solvolysis for cleavage of the internal acetal, reductive elimination was examined. For example, compound **28a**, obtained from **4** by standard procedures, reacted with zinc to give, after protection and saponification, γ,δ unsaturated carboxylic acid **29a**, which underwent smooth iodolactonization. Replacing the iodide of this product with an hydroxyl (**32a** → **32b**) by a free radical process has succeeded albeit in disappointing yield. Nevertheless the resulting hydroxy lactone is a promising synthon of the advanced Kishi−Goto intermediate.

Introduction

Tetrodotoxin[4] is fascinating for several reasons including its awesome toxicity,[5] value as a biological tool,[6] beguiling folklore,[7] and unique architecture.[8] The last item, by itself, provides enough impetus to attempt its synthesis; however, in spite of constant effort,[9] the molecule has succumbed only once, this being the landmark 1972 accomplishment of the Kishi−Goto group.[10] As part of our program for preparing densely functionalized natural products from carbohydrate precursors,[11] we are exploring a synthetic route to tetrodotoxin,[12,13] and in this paper we describe some pertinent developments.

Retrosynthetic Considerations

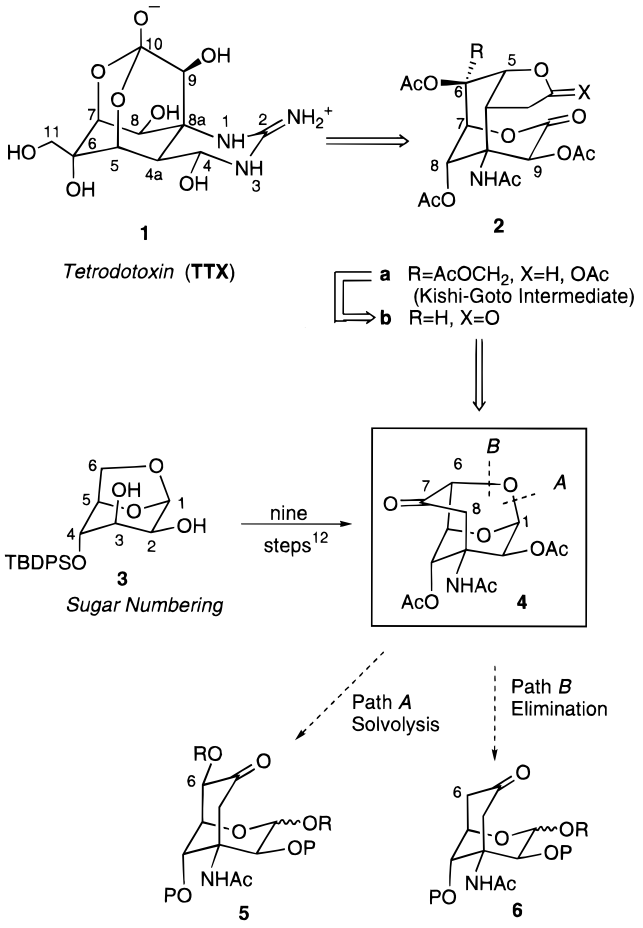
We recently reported upon the preparation of caged molecule **4** in nine steps and 35% yield from 1,6-anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-β-D-mannopyranose, **3**[12] (Scheme 1). Compound **2a** is an advanced intermediate in the Kishi−Goto synthesis,[10] and retron **2b** establishes its relationship to our synthetic intermediate **4**. Two basic operations on precursor **4** are required to obtain synthon **2**: (i) introduction of a properly functionalized two-carbon entity at C8 and (ii) cleavage of the internal acetal. Operations (i) and (ii) could conceivably be carried out in either order, but because of the well-known difficulties of cleaving internal acetals,[14] we decided to address operation (ii) first.

Cleavage of **4** could be effected at A by a solvolytic process to give **5**, or at B by an elimination process to give **6**. Ideally, option A would be preferable since C6 would retain its oxygen functionality, a valuable implement for future manipulations. Much attention was therefore devoted to attempts at acetolysis, and the results have been educational in emphasizing the power-

⊗ Abstract published in *Advance ACS Abstracts,* February 1, 1996.
(1) This project was supported by grants from NIH (GM 51237) and NSF (9311356).
(2) Presented in part by C.S.B. at the Hong Kong International Symposium on Heterocyclic Chemistry, August 1995.
(3) (a) C.S.B.: Synthetic Organic Chemistry Graduate Fellowship Awardee of the Burroughs Wellcome Fund, 1992−1993. (b) R.V.: Feodor Lynen Fellowship from the Alexander von Humboldt Foundation, 1992−1993.
(4) Tetrodotoxin, Saxitoxin and the Molecular Biology of the Sodium Channel. *Ann. N.Y. Acad. Sci.* **1986**, *479,* 1−448. Mosher, H. S.; Fuhran, F. A. In *Seafood Toxins*; Ragelis, E. P., Ed.; ACS Symposium Series 262; American Chemical Society: Washington, DC, 1986; pp 334−344. Kotaki, Y.; Shimizu, Y. *J. Am. Chem. Soc.* **1993**, *115,* 827.
(5) Hucho, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 39. Becker, S.; Gordon, R. D. *Handbook Exp. Pharmocol.* **1992**, *102*, 719. Lazdunski, M.; Renead, J. F. *Annu. Rev. Physiol.* **1982**, *44*, 463. Sutherland, S. K. In *Australian Animal Toxins*; Oxford University Press: Oxford, U.K., 1983. Sheumack, D. D; Howden, M. E. H.; Spencer, I.; Quinn, R. J. *Science* **1978**, *199*, 188.
(6) Booth, W. *Science* **1989**, *240*, 274. Davis, W. *Science* **1989**, *240*, 1715.
(7) Davis, W. *The Serpent and the Rainbow*; Simon and Schuster: New York, 1985.
(8) Woodward, R. B. *Pure Appl. Chem.* **1964**, *9*, 49. Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, *21*, 2059. Tsuda, K.; Ikuma, S.; Kawamura, M.; Tachikawa, R.; Sakai, K.; Tamura, C.; Amakasu, O. *Chem. Pharm. Bull. Jpn.* **1963**, *11*, 1473.
(9) (a) For R. B. Woodward's approach, see: Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1. (b) Yamamoto, N.; Nishikawa, T.; Isobe, M. *Synlett* **1995**, 505 and references therein. (c) Sato, K.; Nagai, Y.; Kajihara, Y.; Nakamura, Y.; Bokura, M.; Yoshimura, J. Abstracts of XVIIth International Carbohydrate Symposium, Ottawa, 1994, Abstract B1.70. Sato, K.; Kajihara, Y.; Nakamura, Y.; Yoshimura, J. *Chem. Lett.* **1991**, 1559 and references therein. (d) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. S.; Roman, R. B.; Ferguson, G.; Parvez, M. *J. Org. Chem.* **1983**, *48*, 3621, 3627.
(10) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217, 9219 and references therein.
(11) McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 3250. Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4048.
(12) Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666.
(13) Burgey, C. S.; Vollerthun, R.; Fraser-Reid, B. *Tetrahedron Lett.* **1994**, *35*, 2637.
(14) Hall, H. K., Jr.; DeBlauwe, Fr. *J. Am. Chem. Soc.* **1975**, *97*, 655. Cerny, M.; Stanek, J. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 24. Cerny, M.; Pacak, J.; Stanek, J. *Collect. Czech. Chem. Commun.* **1965**, *30*, 1151. Carlson L. J. *J. Org. Chem.* **1965**, *30*, 3953.

0022-3263/96/1961-1609$12.00/0

Scheme 1



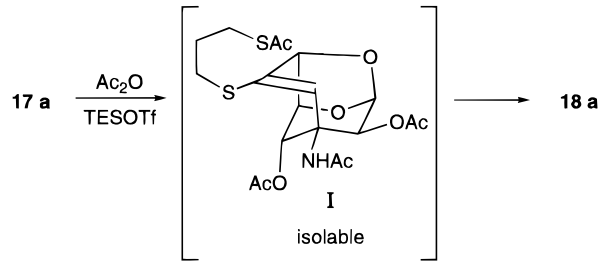
ful influence (i.e., *armed/disarmed* effects)[15] that protecting groups can have upon this cleavage reaction and, furthermore, in sensitizing us to the threatening specter of adamantyl expansion in manipulating these densely-functionalized systems (*vide infra*).

Acetolysis Reactions

We first applied solvolytic conditions using triethylsilyl trifluoromethanesulfonate and acetic anhydride that had been demonstrated previously in our laboratory. Thus as indicated in Table 1, acetolysis of disarmed ketone **4** and its methylene counterpart **7** failed to produce **8a** or **8b**, respectively, which would have resulted from cleavage of their 1,6-anhydro rings. By contrast, when the ester protecting groups were replaced with benzyl ethers as in **9a** and **9b**, the resulting disarmed species underwent cleavage. However the products were the adamantane-like structures **10a** and **10b**, respectively.

Armed/disarmed effects were also evident in the acetolyses of the protected carbinols obtained by reducing ketones **4** and **9a**. Although the 7*R* triacetate and tribenzyl derivatives **11a** and **11b** were both solvolyzed to give adamantane-like structures **12a** and **12b**, respectively, the triacetate reacted 240 times slower than the tribenzyl analog. A substantial rate difference was also observed with the 7*S* counterparts **13** and **15**, even though the products were the bicyclic species **14** and **16**, respectively. Dramatic rate differences were also observed between the armed/disarmed thioketals **17a** and **17b** in their reactions to give the thioenols **18a** and **18b**, respectively. In all of the examples in Table 1, the benzyl ether derivatives not only reacted faster than the acetylated analogues but also gave better yields.

In the case of thioketal **17a** there appears to be competition between the acetal and the thioacetal for Ac^+. This idea gained support from isolation of a vinyl sulfide identified as **I** on the bases of its (a) ^{1}H NMR and mass spectra and (b) conversion into **18a** by further acetolysis.[16]



The results in Table 1 may be summarized as depicted in Scheme 2 which, in turn, are based upon our rationalizations of the armed/disarmed effect in glycoside hydrolysis.[17] Thus it may be assumed that solvolysis of the tricyclic acetal **II** proceeds *via* acetyl oxonium ion **III** and then to oxocarbenium ion **IV**. An electron-withdrawing group at C7 and/or C2 (i.e., R′ = EWG) deters progress of the reaction by a combination of early and late transition state effects, first, by draining electron density from O6, thereby inhibiting the formation of **III**, and subsequently by disfavoring the incipient oxocarbenium ion **IV** which is expected to be destablized when R′ = Ac.

When Y is non-nucleophilic, bicyclic products are obtained which result from elimination (e.g., **14**) or intermolecular trapping of the oxocarbenium ion **IV** by acetate (**16** and **18**). However, the process of adamantyl expansion (**IV** → **VII**) is favored when substituent Y is nucleophilic, as in the C7(*R*) benzyl ether **11b** (Table 1). For the trigonal substrates **9a** and **9b**, the expansion reaction may be envisaged as the synchronous Prins-like process depicted in **VI**.

Elimination Reactions

The results in Table 1 and Scheme 2 clearly discouraged pursuit of the acetolysis route (path A, Scheme 1). The elimination alternative (path B, Scheme 1) requires an amenable synthon at C7. The approach in Scheme 3 was adopted in which a β-elimination process to cleave bond B was envisaged. Accordingly, it was necessary to replace the acetyl groups of **4** with benzyl ethers. The benzylation step in the conversion of **4** into **9a** proved to be most demanding, requiring specific reaction conditions in order to avoid formation of side products (see Experimental Section). The Levine reagent[18] was used to provide enol ether **19** as a mixture of *E*/*Z* isomers. Treatment with dilute hydrochloric acid at elevated temperature produced α-enal **20a** in virtually quantitative yield, and PMB glycosidation afforded **20b**. The path

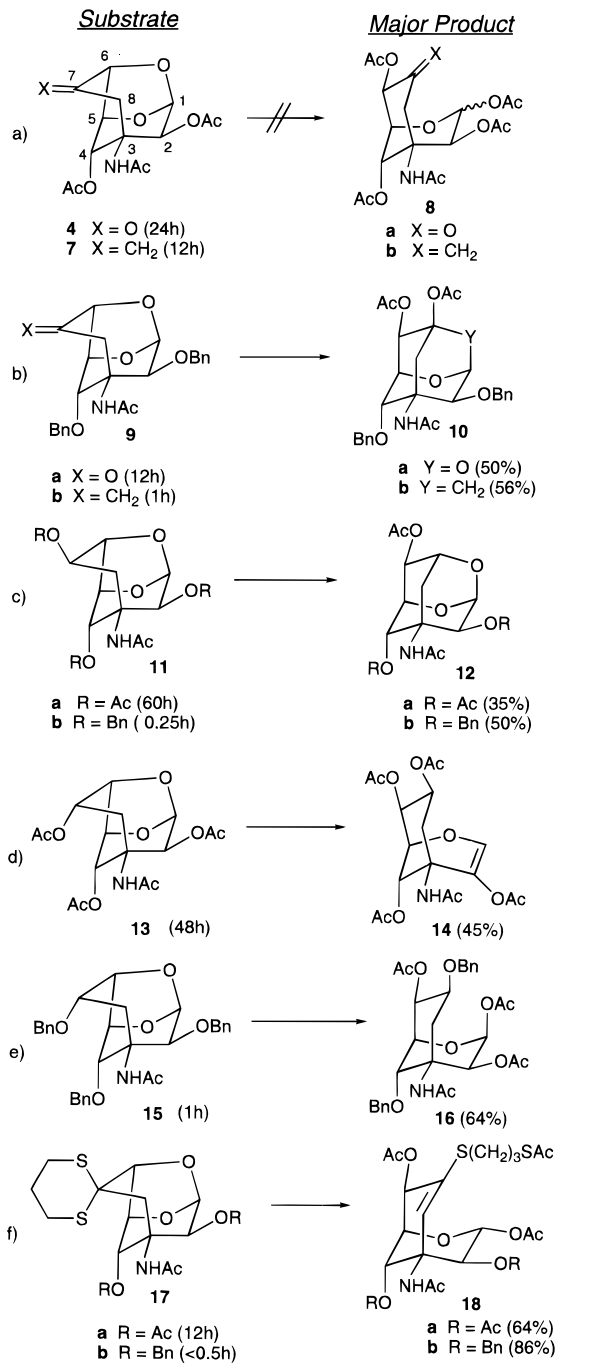
(15) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.

(16) Transformations similar to **17a** → **I** have been observed for other thioketals.

(17) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068.

(18) (a) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150. (b) Earnshaw, C.; Wallis, C. J.; Warren, S. J. *J. Chem. Soc., Chem. Commun.* **1977**, 314 and references therein.

Table 1. Acetolysis of Some Armed and Disarmed Tricyclic Acetals[a]



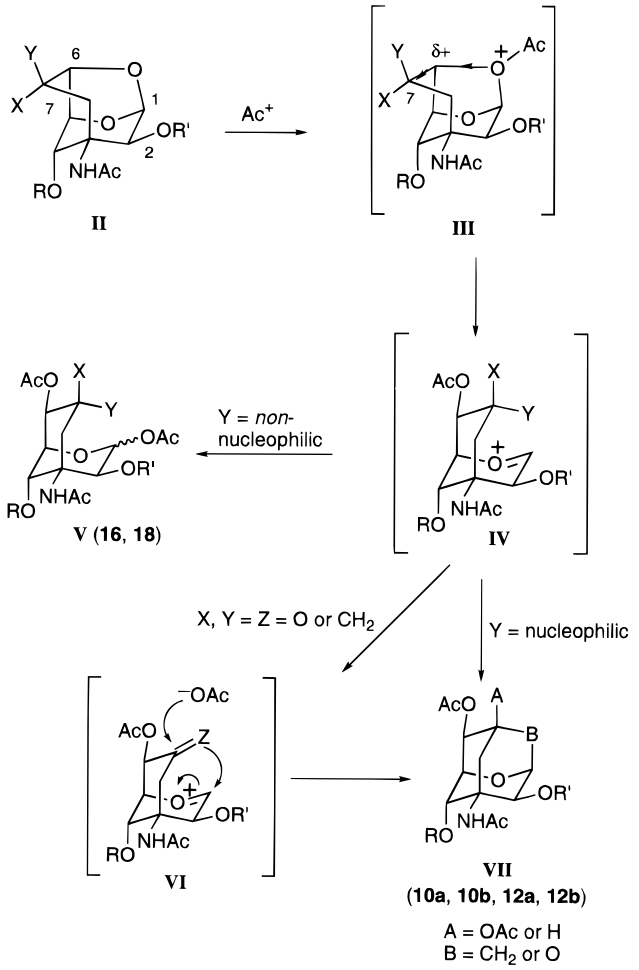
[a] Yields are not optimized.

chosen for installing the C6 oxygen proceeded *via* allylic alcohol **20c** to epoxy alcohol **21a,** which was converted into iodo epoxide **21b**. All of these transformations proceeded in excellent yields, as did the succeeding steps of reductive elimination to **22a**, silylation to **22b**, and finally ozonolysis to **22c**.

The next requirement was a 2-carbon entity at C8, and an allyl group seemed a promising synthon. However attempts at alkylating **22c** by use of 6 equiv of LDA resulted in allylated acetamide **23** as the only isolable product. A nonanionic procedure was evidently required for C8 allylation, and it seemed best to address this issue as early as possible into the synthesis.

We therefore needed to retool our strategy, and in so doing we were mindful of another problem, *viz*. the length

Scheme 2



of the β-elimination route **4** → **19** → **20**. The alternative of reductive elimination promised to be more expedient. The use of zinc or samarium(II) iodide[19] was appealing, and a model experiment with the latter reagent was performed on ketone **4** (Scheme 4). Thus with 4 equiv of samarium(II) iodide and ketone **4**, the product proved to be dioxaadamantane **25a**, similar to **10a** already encountered in Table 1. This result implied the intermediacy of samarium enolate **24**, but attempts at trapping with various electrophiles failed, as did attempts to hydrolyze, reduce, or oxidize **25a** to a bicyclic species.

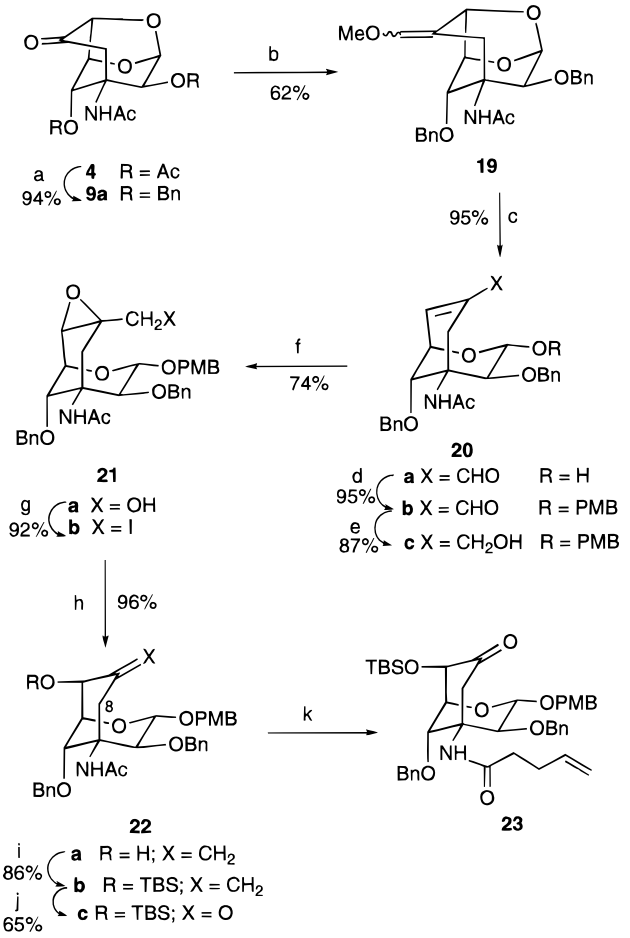
These model studies indicated that a C7 carbonyl group was undesirable, in that its presence invariably led to stable, adamantane-like tricyclic structures. Replacement with an iodide would still permit the use of samarium(II) iodide and/or zinc, and hence compound **4** was processed with this in mind (Scheme 5).

In order to avoid products such as **23**, a nonanionic procedure for C8-alkylation was required, and the Keck reaction[20] was applied. Thus bromination of **4** with pyridinium bromide perbromide followed by reaction with allyltributyltin gave **26a** and its C8-epimer as a 4:1 mixture in 57% overall yield. Assignment of the major product as **26a** was based on the observation of an NOE (14%) between H4 and H8 (Scheme 5). Reduction of the

(19) Pratt, D. K.; Hopkins, B. P. *Tetrahedron Lett.* **1987**, *28*, 3065. Hanessian, S.; Girard, C.; Chiara, J. L. *Tetrahedron Lett.* **1992**, *33*, 573. Enholm, E. J.; Jiang, S. *Hetereocycles* **1992**, *34*, 2244.

(20) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. Keck, G. E.; Enholm, E. J.; Yates, J. B; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

Scheme 3



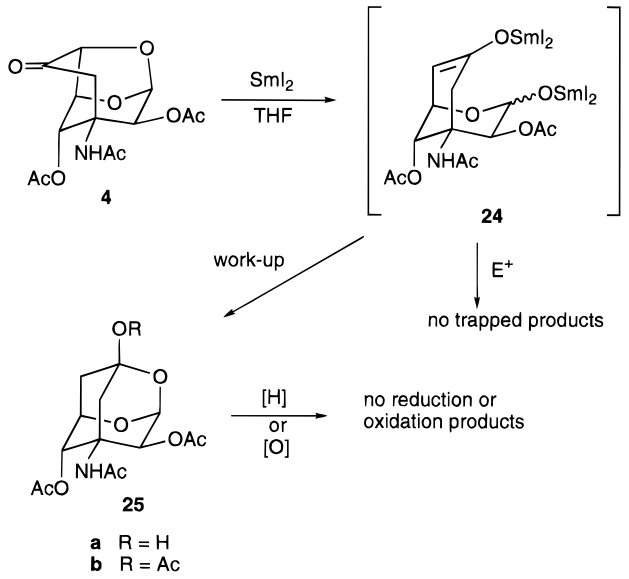
a) NaOMe; NaH, BnBr, THF:DMF (20:1); b) (methoxymethylene)-triphenylphosphorane, THF; c) 1N HCl:THF (1:6); d) PMBOH, Amberlyst 15 ion-exchange, THF; e) $NaBH_4$, $CeCl_3$, EtOH:H_2O (2:1); f) MCPBA, $NaHCO_3$, CH_2Cl_2; g) I_2, imidazole, Ph_3P, $PhCH_3$; h) Zn, EtOH; i) TBSOTf, Et_3N, CH_2Cl_2; j) O_3, pyridine, CH_2Cl_2:MeOH (1:1); Me_2S; k) LDA, THF; HMPA, allyl bromide.

corresponding di-*O*-benzyl analog, **26b**, with sodium borohydride gave **27a** as the major isomer, and Garegg's iodination procedure[21] was used to obtain iodide **27b**.

C7/C8 Furano Moiety

It seemed ideal to use the C8 entity to establish the *syn* C7-OH, and with this in mind, **27b** was subjected to ozonolysis under the Schreiber conditions[22] which led to desired methyl ester[23] **28a** along with a substantial amount of corresponding aldehyde **28b**. Treating the former with zinc in ethanol at reflux caused reductive elimination to alkene **29a** from which the *p*-methoxybenzyl glycoside **29b** was prepared. Epoxidation of this material to **30** would have provided a route to the desired C7-OH *via* intramolecular displacement leading to **32b**. However the double bond of **29b** proved to be very unreactive toward epoxidation; thus with either trifluoroperoxyacetic acid[24] or dimethyldioxirane[25] only a 10% yield of **30** could be achieved.

Scheme 4



Iodolactonization was an alternative for installing the properly oriented C7-OH; but when the process was applied to ester **29b**, iodohydrin **31** (structure not assigned) was the only outcome. Fortunately the corresponding carboxylic acid **29c** reacted smoothly in the presence of iodonium dicollidine perchlorate[26] as promoter, to give **32a** in high yield.

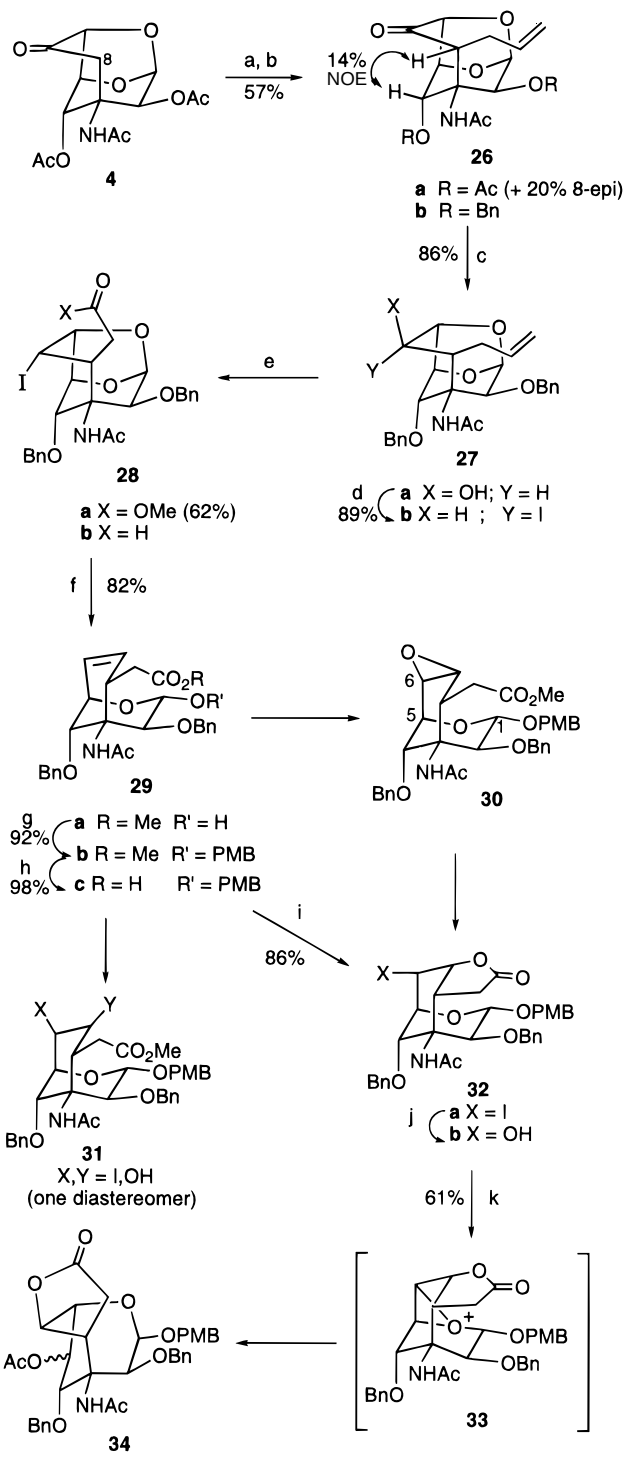
RI → R• → ROH

The task of replacing the C6-I with an hydroxy group, i.e., **32a** → **32b**, was now addressed. Attempts at solvolysis under the relatively mild conditions of silver trifluoroacetate in aqueous acetone at reflux afforded good yields of ring-expanded product **34**. Participation of the ring oxygen *anti*-periplanar to a leaving group, with resultant formation of an *epi*-oxonium, e.g., **33**, ion is frequently encountered in pyranoside systems, but the outcome is usually ring contraction.[27] The ease of the expansion leading to **34** is undoubtedly due to the ideal *anti*-periplanar relationship that exists between oxygen and iodine, which facilitates formation of intermediate **33**.

Free radical methods should not encounter such dire consequences; but procedures for the use of TEMPO[28] were unavailing. We were aware of a timely report by Nakamura and co-workers[29] in which organic halides were converted into the corresponding alcohols by oxygenation in the presence of air at 0−20 °C. When these conditions were applied to the readily available 6-deoxy-

(21) Garegg, P. J. *Pure Appl. Chem.* **1984**, *56*, 845.
(22) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.
(23) For an alternative procedure, see: Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, 643. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.
(24) Heaney, H. *Aldrichimica Acta* **1993**, *26*, 35.
(25) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
(26) Carlsohn, H. *Ber. Deutsch. Chem. Ges.* **1935**, *68*, 2209. Carlsohn, H. *Angew. Chem.* **1933**, *46*, 747. Lemieux, R. U.; Morgan, A. K. *Can. J. Chem.* **1965**, *43*, 2190.
(27) Aspinall, G. O.; Chattejree, D.; Khondo, L. *Can. J. Chem.* **1984**, *62*, 2728. Kanai, K.; Zelle, R. E.; Sham, H.; Grieco, P. A.; Callant, P. *J. Org. Chem.* **1984**, *49*, 3867. Alslani-Shotorbani; Buchanan, J. G.; Edgar, A. R.; Shanks, G. T.; Williams, G. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2267. Capon, B. *Chem. Rev.* **1969**, *69*, 407. Mootoo, D. R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1570.
(28) Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 7902. Howell, A. R.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1990**, *2*, 103. Barrett, A. G. M.; Bezuidenhoudt, C. B.; Melcher, L. M. *J. Org. Chem.* **1990**, *55*, 5196. Barrett, A. G. M.; Rys, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 837.
(29) Nakamura, E.; Inubushi, T.; Aoki, S.; Machili, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980. Nakamura, E.; Sato, K.; Imanishii, Y. *Synlett* **1995**, 525.

Scheme 5



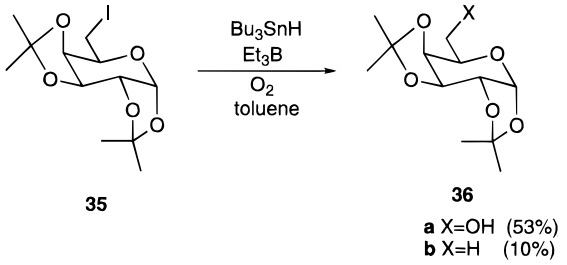
a) pyridinium bromide perbromide, AcOH; b) allyltributyltin, AIBN, PhH; c) $NaBH_4$, EtOH; d) I_2, Ph_3P, imidazole, $PhCH_3$; e) O_3, CH_2Cl_2/MeOH (5:1); Et_3N, Ac_2O, CH_2Cl_2; f) Zn, EtOH; g) PMBCl, Ag_2O, TBAI, DMF; h) LiOH, MeOH/H_2O (3:1); i) IDCP, CH_3CN; j) O_2, Bu_3SnH, Et_3B, $PhCH_3$; k) silver trifluroacetate, acetone:H_2O (3:1).

6-iodogalactose **35**[30] (Scheme 6), there was no success. However, modification[31] involving the use of triethylborane and a stream of molecular oxygen caused the desired replacement, alcohol **36a** being obtained in 53% yield, with only minor amounts of the reduced material **36b**. A small amount of starting material (approximately 10%) was also recovered.

(30) Schmidt, O. Th. *Methods Carbohydr. Chem.* **1962**, *1*, 191.

(31) For another modification which employs AIBN at 60 °C, see: Moutel, S.; Prandi, J. *Tetrahedron Lett.* **1994**, *35*, 8163.

Scheme 6



Application of these conditions to substrate **32a** afforded the desired material **32b** but with a disappointing recovery (77%) of the starting material. Thus there had been only 11% conversion of **32a** into **32b**.

Conclusion

We have accomplished a synthesis of lactone **32b**, even though the efficiency of the final iodide to hydroxyl conversion needs to be improved. Compound **32b** correlates well with **2b**, a synthon for the Kishi−Goto intermediate **2a** (Scheme 1). In the course of this study we have become aware of powerful armed/disarmed effects which influence the acetolysis of 1,6-anhydro pyranoses and of the constant threat of adamantyl expansion, e.g., **II** → **VII** (Scheme 2), of these tricyclic acetals. Although initially regarded as disappointments, these transformations could conceivably be gainfully exploited to facilitate a synthesis of TTX, **1**. Our current efforts are directed along these lines.

Experimental Section

For general procedures, see ref 12.

Standard Acetolysis Procedure. The substrate (20 μmol) was dissolved in acetic anhydride (2 mL) under argon at 0 °C, and triethylsilyl trifluoromethanesulfonate (9 μL, 40 μmol) was added. The solution was stirred at 0 °C for the specified time, allowed to warm to room temperature, and kept there until TLC showed the disappearance of the substrate. Further additions of reagents were made, if necessary, to bring the reaction to completion, or to ensure that the substrate was inert. Saturated aqueous $NaHCO_3$ solution (~12 mL) was added, CH_2Cl_2 was used for extraction, and the organic layers were dried and concentrated. The residue was then chromatographed with the stated solvent system.

Preparation of Solvolysis Substrates for Table 1. *N*-[(1*S*,3*S*,6*R*,7*S*,8*S*,10*S*)-7,10-Bis(benzyloxy)-4-oxo-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (9a). Ketone **4** (2.42 g, 7.40 mmol) was disolved in dry methanol (50 mL), and NaH (30 mg of 60% dispersion in mineral oil) was added slowly. After 15 min the reaction mixture was neutralized with Amberlite IRC-50S ion-exchange resin and filtered, and the resin was rinsed with methanol. The filtrate was concentrated, diluted with toluene, and concentrated. The crude diol was diluted with THF (120 mL) and DMF (6 mL), and sodium hydride (888 mg of 60% dispersion in mineral oil, 22.2 mmol) was added slowly. After 10 min, benzyl bromide (1.89 mL, 15.9 mmol) and tetrabutylammonium iodide (270 mg, 0.74 mmol) were added. The reaction was quenched after 8.5 h by the addition of saturated aqueous NH_4Cl (50 mL), and the solution was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (70 mL), dried, and concentrated. The residue was chromatographed with 30−50% ethyl acetate/petroleum ether (to give 2.55 g **9a**) followed by 100% ethyl actetate to give 260 mg of incompletely benzylated products which were resubjected to the benzylation reaction: THF (20 mL), NaH (62 mg, 1.56 mmol), BnBr (0.112 mL), TBAI, for 24 h affording additional **9a** (2.93 g total,

94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 3H), 2.98 (d, J = 17.6 Hz, 1H), 3.48 (d, J = 17.6 Hz, 1H), 3.65 (bs, 1H), 4.10 (d, J = 6.4 Hz, 1H), 4.41 (d, J = 3.0 Hz, 1H), 4.43 (d, J = 12.3 Hz, 1H), 4.59 (bs, 2H), 4.61 (dd, J = 3.0 Hz, J = 6.4 Hz, 1H), 4.91 (d, J = 12.3 Hz, 1H), 5.01 (s, 1H), 5.67 (d, J = 1.4 Hz, 1H), 7.27−7.51 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.87, 40.86, 58.51, 72.47, 72.56, 74.07, 75.35, 78.91, 100.42, 128.01, 128.50, 128.61, 128.89, 129.13, 137.02, 137.67, 169.68, 203.38; GC/MS (NH_3) m/z 441 $(M + NH_4)^+$, 424 $(MH)^+$; $[\alpha]^{20}_D = -98.2°$ (c 0.5, $CHCl_3$); HRMS calcd for $C_{24}H_{25}NO_6$ 424.1753, found 424.1755.

***N*-[(1*R*,3*R*,4*R*,6*R*,7*S*,8*R*,10*S*)-7,10-Diacetoxy-4-methylene-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (9b).** Methyltriphenylphosphonium iodide (91 mg, 224 μmol) was suspended in THF (5 mL), and *n*-BuLi (100 μL of a 2.0 M solution in THF, 200 μmol) was added at −10 °C. The solution was allowed to warm to rt and stirred for 1 h, and then **9a** (21 mg, 50 μmol), dissolved in THF (2 mL), was added. After 10 h the reaction was quenched by the addition of acetone. The solution was adsorbed onto silica gel and filtered through a pad of silica with Et_2O and concentrated, and the residue was chromatographed with 30% ethyl acetate/hexanes (17 mg, 79%, colorless syrup): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, 3H), 2.90 (d, J = 16.1 Hz, 1H), 3.20 (ddd, J = 2.2 Hz, J = 2.2 Hz, J = 16.1 Hz, 1H), 3.56 (bs, 1H), 4.33 (d, J = 2.6 Hz, 1H), 4.40−4.49 (m, 3H), 4.52 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.86 (d, J = 12.3 Hz, 1H), 4.99 (s, 1H), 5.02 (bs, 1H), 5.08 (bs, 1H), 5.47 (m, 1H), 7.25−7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.07, 32.72, 58.19, 72.02, 72.27, 74.24, 75.41, 78.77, 79.38, 98.76, 113.99, 127.68, 127.85, 128.33 128.52, 128.60, 128.97, 137.48, 138.35, 139.97, 169.56; GC/MS (NH_3) m/z 587 $(M + NH_4)^+$; 422 $(MH)^+$; $[\alpha]^{20}_D = -119.9°$ (c 0.5, $CHCl_3$); HRMS calcd for $C_{25}H_{27}NO_5$ 422.1960, found 422.1969.

***N*-[(1*S*,3*S*,4*S*,5*S*,7*R*,8*S*,9*S*)-7,8-Diacetoxy-4,9-bis(benzyloxy)-2-oxatricyclo[3.3.1.1^{3,7}]dec-5-yl]acetamide (10b).** Compound **9b** (19 mg, 45 μmol) was subjected to the standard acetolysis conditions, and after 1 h at 0 °C, TLC indicated completion. Workup and chromatography with 30−40% ethyl acetate/hexanes afforded **10b** (12 mg, 56%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3H), 1.96 (s, 3H), 2.14 (s, 3H), 2.30 (ddd, J = 2.2 Hz, J = 2.2 Hz, J = 12.5 Hz, 1H), 2.61 (bd, J = 12.5 Hz, 1H), 2.71 (d, J = 12.5 Hz, 1H), 2.80 (dd, J = 2.0 Hz, J = 12.5 Hz, 1H), 3.97 (d, J = 3.9 Hz, 1H), 4.14 (m, 1H), 4.30 (ddd, 1H), 4.42 (d, J = 11.9 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.9 Hz, 1H), 4.81 (d, J = 1.7 Hz, 1H), 5.19 (m, 1H), 5.41 (s, 1H), 7.20−7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.11, 22.11, 24.08, 28.37, 33.34, 58.40, 69.74, 71.11, 72.02, 72.54, 72.64, 72.71, 76.12, 76.18, 127.61, 128.31, 128.46, 128.95, 137.63, 138.19, 169.70, 169.97, 170.11; GC/MS (NH_3) m/z 524 $(MH)^+$; $[\alpha]^{20}_D = -32.90°$ (c 0.3, $CHCl_3$); HRMS calcd for $C_{29}H_{33}NO_8$ 524.2275, found 524.2203.

***N*-[(1*R*,3*R*,4*R*,6*R*,7*S*,8*S*,10*S*)-4,7,10-Triacetoxy-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (11a) and Its 4-Epimer (13).** Compound **4** (48 mg, 148 μmol) was dissolved in EtOAc (10 mL), PtO_2 (9.6 mg) was added, and the mixture was hydrogenated in a Paar apparatus (50 psi). After 9 h the reaction was complete. The reaction was filtered and concentrated, and the residue was chromatographed on silica gel with EtOAc to give (40 mg, 85%) a colorless syrup. The separation of the two alcohol products was only possible in part. Samples of 4*R* and 4*S* isomers were acetylated in the usual way to give **11a** and **13**. For **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.17 (s, 6H), 2.30 (s, 3H), 2.45 (dd, J = 8.8 Hz, J = 13.4 Hz, 1H), 2.91 (dd, J = 8.7 Hz, J = 13.4 Hz, 1H), 4.52 (d, J = 6.2 Hz, 1H), 4.91 (dd, J = 3 Hz, J = 6.2 Hz, 1H), 5.08 (bs, 1H), 5.25 (dd, J = 8.7 Hz, J = 8.8 Hz, 1H), 5.38 (bs, 1H), 5.70 (d, J = 3.0 Hz, 1H), 6.27 (s, 1H). For **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 2.22 (s, 3H), 2.59 (d, J = 15.6 Hz, 1H), 2.71 (dd, J = 6.6 Hz, J = 15.6 Hz, 1H), 4.37 (m, 1H), 4.93 (dd, J = 3.2 Hz, J = 6.0 Hz, 1H), 5.01−5.04 (m, 1H), 5.28 (d, 1.9 Hz, 1H), 5.31−5.36 (m, 1H), 6.00 (d, J = 3.2 Hz, 1H), 6.15 (s, 1H).

***N*-[(1*R*,3*R*,4*R*,6*R*,7*S*,8*S*,10*S*)-4,7,10-Tris(benzyloxy)-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (11b) and Its 4-Epimer (15).** The mixture of alcohols from reduction and deacetylation (NaOMe, MeOH) of **4** above (16 mg, 65 μmol) was dissolved in DMF under argon. Sodium hydride (10.3 mg, 259 mmol, 60% suspension) was added, and 5 min later BnBr was added. After 5 h the reaction was quenched by addition of saturated aqueous NH_4Cl, and the solution was processed and chromatographed to give **15** (9.5 mg, 28%) and **11b** (11.9 mg, 35%). For **11b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.48 (dd, J = 8.6 Hz, J = 13.2 Hz, 1H), 2.64 (ddd, J = 8.2 Hz, J = 13.2 Hz, 1H), 3.55 (bs, 1H), 3.72 (dd, J = 8.2 Hz, J = 8.6 Hz, 1H), 4.33−4.45 (m, 4H), 4.50 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.89 (d, J = 12.4 Hz, 1H), 4.98 (s, 1H), 5.50 (d, J = 1.4 Hz, 1H), 7.26−7.48 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.01, 30.44, 58.93, 70.62, 70.81, 71.78, 72.28, 72.47, 73.31, 78.31, 98.60, 127.67, 127.80, 128.35, 128.41, 128.63, 128.66, 129.00, 137.48, 138.05, 138.25, 169.68; GC/MS (NH_3) m/z 516 $(MH)^+$; $[\alpha]^{20}_D = -94.6°$ (c 0.5, $CHCl_3$); HRMS calcd for $C_{31}H_{33}NO_6$ 516.2377, found 516.2375. For **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 3H), 2.58−2.63 (m, 2H), 3.56 (bs, 1H), 4.04 (m, 1H), 4.25 (dd, J = 4.4 Hz, J = 6.0 Hz, 1H), 4.32 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 12.5 Hz, 1H), 4.43 (dd, J = 3.2 Hz, J = 6.0 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 12.5 Hz, 1H), 4.99 (s, 1H), 5.03 (d, J = 3.2 Hz, 1H), 5.40 (d, J = 1.4 Hz, 1H), 7.23−7.48 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.21, 29.33, 57.79, 70.97, 72.13, 72.36, 72.90, 73.55, 74.41, 75.15, 78.68, 98.80, 127.63, 127.70, 128.00, 128.30, 128.42, 128.54, 128.59, 128.96, 137.50, 137.98, 138.49, 169.46; GC/MS (NH_3) m/z 516 $(MH)^+$; $[\alpha]^{20}_D = -90.3°$ (c 0.5, $CHCl_3$); HRMS calcd for $C_{31}H_{33}NO_6$ 516.2377, found 516.2399.

***N*-[(1*R*,3*R*,5*S*,6*S*,7*R*,9*R*,10*S*)-6,9,10-Triacetoxy-2,4-dioxatricyclo[3.3.1.1^{3,7}]dec-7-yl]acetamide (12a).** Compound **11a** (13 mg, 35 μmol) was subjected to the standard acetolysis procedure at 0 °C and warmed to rt. After 24 h the addition was repeated, no change being observed after 48 h. After workup the residue was chromatographed on silica gel with 80% EtOAc/hexane to give 8 mg (65%) of a brown syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3H), 2.06 (s, 3H), 2.18 (s, 3H), 2.68 (d, J = 12.8 Hz, 1H), 3.08 (d, J = 12.8 Hz, 1H), 3.86 (d, J = 2.0 Hz, 1H), 4.31 (dd, J = 1.9 Hz, J = 1.8 Hz, 1H), 4.43−4.62 (m, 3H), 4.85 (d, J = 12.0 Hz, 1H), 4.95 (d, J = 1.8 Hz, 1H), 5.29 (d, J = 1.9 Hz, 1H), 5.34 (bs, 1H), 5.40 (d, J = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.92, 21.66, 23.91, 32.48, 57.02, 68.03, 70.88, 72.11, 72.27, 72.55, 75.34, 94.36, 97.70, 137.26, 137.77, 167.47, 170.02, 170.88; GC/MS (NH_3) m/z 526 $(MH)^+$.

***N*-[(1*R*,3*R*,5*S*,6*S*,7*R*,9*R*,10*S*)-9-Acetoxy-6,10-bis(benzyloxy)-2,4-dioxatricyclo[3.3.1.1^{3,7}]dec-7-yl]acetamide (12b).** Compound **11b** (19 mg, 45 μmol) was subjected to the standard acetolysis procedure at 0 °C for 1 h. Workup and chromatography on silica gel with 30−40% EtOAc/hexane gave **12b** (11.4 mg, 48%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3H), 2.19 (s, 3H), 2.45 (d, J = 3.0 Hz, 1H), 3.91 (d, J = 2.2 Hz, H1), 4.17 (m, 1H), 4.20 (m, 1H), 4.44 (d, J = 12.0 Hz, H1), 4.51 (d, J = 11.7 Hz, H1), 4.59 (bs, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.84 (bs, 1H), 5.20 (d, J = 2.2 Hz, 1H), 5.31 (s, 1H), 7.22−7.48 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.21 24.05, 29.38, 55.19, 68.86, 71.32, 72.09, 72.23, 72.56, 75.86, 77.24, 91.87, 127.63, 127.76, 128.38, 128.46, 128.59, 128.99, 137.49, 137.94, 170.18, 170.93; GC/MS (NH_3) m/z 468 $(MH)^+$; $[\alpha]^{20}_D = -99.6°$ (c 0.4, $CHCl_3$); HRMS calcd for $C_{26}H_{29}NO_7$ 468.2014, found 468.2040.

***N*-[(1*S*,5*R*,7*S*,8*R*,9*S*)-4,7,8,9-Tetraacetoxy-2-oxabicyclo-[3.3.1]non-3-en-5-yl]acetamide (14).** Compound **13** (8 mg, 22 μmol) was subjected to the standard acetolysis conditions and after 1 h at 0 °C the mixture was warmed to rt. After 6 and 24 h, additional TESOTf (13 μL, 57 μmol; 20 μL, 48 μmol) was added. The reaction was then processed and the residue chromatographed with 10, 15, and 50% acetone/CH_2Cl_2, yielding a 9:1 mixture of **14** and starting material as judged by ^{1}H NMR (4 mg, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.00 (m, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.23 (s, 3H), 2.56 (dd, J = 6.3 Hz, J = 13.2 Hz, 1H), 2.72 (dd, J = 11.0 Hz, J = 13.2 Hz, 1H), 4.65 (dd, J = 2.1 Hz, J = 3.3 Hz, 1H), 5.15 (dd, J = 3.3 Hz, J = 10.1 Hz, 1H), 5.52 (ddd, J = 6.3 Hz, J = 10.1 Hz, J = 11.0 Hz, 1H), 5.80 (s, 1H), 5.82 (d, J = 2.1 Hz, 1H), 6.63

(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.55, 20.79, 20.89, 24.23, 34.35, 54.51, 65.74, 73.14, 74.24, 126.77, 138.24, 169.64, 169.82, 169.97, 170.28, 170.49; GC/MS (NH_3) *m/z* 431 (M + NH_4)$^+$, 414 (MH)$^+$; HRMS calcd for $C_{18}H_{23}NO_{10}$ 414.1393, found 414.1400.

***N*-[(1*S*,3*S*,4*S*,5*R*,7*S*,8*R*,9*S*)-3,4,8-Triacetoxy-7,9-bis(benzyloxy)-2-oxabicyclo[3.3.1]non-5-yl]acetamide (16).** Compound **15** (9.7 mg, 18.8 μmol) was subjected to the standard acetolysis procedure at 0 °C for 30 min. Workup and chromatography on silica gel with 40−50% EtOAc/hexane yielded pure **16** (6.9 mg, 64%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.85 (m, 1H), 2.08 (m, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 2.25 (dd, J = 3.2 Hz, J = 15.7 Hz, 1H), 3.93 (ddd, J = 3.2 Hz, J = 3.2 Hz, J = 3.2 Hz, 1H), 4.48 (d, J = 10.9 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.84 (d, J = 10.9 Hz, 1H), 5.0 (d, J = 3.2 Hz, 1H), 5.30 (dd, J = 3.2 Hz, J = 3.2 Hz, 1H), 5.48 (d, J = 3.2 Hz, 1H), 5.57 (m, 1H), 6.21 (d, J = 3.2 Hz, 1H), 6.35 (s, 1H), 7.27−7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.94, 21.11, 21.37, 24.36, 27.01, 63.96, 65.86, 72.41, 73.47, 74.55, 75.55, 77.24, 83.31, 100.39, 127.76, 127.90, 127.95, 128.39, 128.64, 128.73, 136.96, 137.85, 170.07, 170.46; GC/MS (NH_3) *m/z* 587 (M + NH_4)$^+$, 570 (MH)$^+$, 510 (MH − HOAc)$^+$; $[\alpha]^{20}_D$ = −30.8° (*c* 0.39, $CHCl_3$); HRMS calcd for $C_{30}H_{35}NO_{10}$ 570.2329, found 570.2316.

***N*-[(1*S*,3*S*,6*R*,7*S*,8*S*,10*S*)-7,10-Diacetoxy-4,4-(1′,5′-dithiapentane-1′,5′-diyl)-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (17a).** Compound **4** (1.89 g, 5.76 mmol) was dissolved in CH_2Cl_2 (200 mL), and 1,3-propanedithiol (1.78 mL, 17.3 mmol) and BF_3·OEt_2 (2.3 mL, 17.3 mmol) were added. After stirring for 12 h, benzaldehyde (1.24 mL, 12.1 mmol) was added, and after another 10 h, the mixture was extracted with saturated aqueous $NaHCO_3$ (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were dried, filtered, and concentrated. Chromatography with 0−25% acetone/CH_2Cl_2 (linear gradient) yielded pure **17a** (2.28 g, 94%) as a colorless syrup: mp 258−268 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H), 1.92−2.13 (m, 2H), 2.15 (s, 3H), 2.25 (s, 3H), 2.52 (d, J = 15.1 Hz, 1H), 2.73−2.85 (m, 2H), 2.97 (d, J = 15.1 Hz, 1H), 2.98−3.19 (m, 2H), 4.84 (d, J = 6.0 Hz, 1H), 5.00 (dd, J = 3.1 Hz, J = 6.0 Hz, 1H), 5.10 (bs, 1H), 5.31 (d, J = 1.9 Hz), 6.15 (s, 1H), 6.42 (d, J = 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.93, 21.23, 24.18, 27.65, 27.80, 38.73, 46.45, 57.91, 68.17, 73.18, 73.97, 77.18, 99.36, 169.39, 169.68, 172.63; GC/MS (NH_3) *m/z* 435 (M + NH_4)$^+$, 418 (MH)$^+$; $[\alpha]^{20}_D$ = −68.8° (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{17}H_{23}NO_7S_2$ 418.0988, found 418.0977.

***N*-[(1*S*,3*S*,6*R*,7*S*,8*S*,10*S*)-7,10-Bis(benzyloxy)-4,4-(1′,5′-dithiapentane-1′,5′-diyl)-2,9-dioxatricyclo[4.3.1.0^{3,8}]-dec-6-yl]acetamide (17b).** Compound **17a** (749 mg, 1.79 mmol) was dissolved in MeOH (100 mL), and a catalytic amount of NaH was added. After 30 min the reaction was neutralized with Amberlite ion-exchange resin 1RC-50S. The solution was filtered and concentrated, and after azeotroping with toluene (2×), the crude diol (592 mg) was dissolved in DMF (100 mL) under argon. Sodium hydride (287 mg, 7.17 mmol, 60% suspension) and 20 min later BnBr (0.636 mL, 5.38 mmol) were added, and the mixture was stirred for 10 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the solution was concentrated, diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried, filtered, and concentrated. The crude product was adsorbed onto silica gel and chromatographed with 10−50% EtOAc/hexane (linear gradient) to give **17b** (900 mg, 98%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.85−2.13 (m, 2H), 2.62 (d, J = 11.8 Hz, 1H), 2.72−2.82 (m, 2H), 2.73 (d, J = 14.8 Hz, 1H), 2.98 (m, 1H), 3.15 (m, 1H), 3.63 (bs, 1H), 4.37 (d, J = 12.4 Hz, 1H), 4.52 (dd, J = 3.2 Hz, J = 5.9 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 5.9 Hz, 1H), 4.85 (s, 1H), 4.91 (d, J = 12.4 Hz, 1H), 5.38 (d, J = 3.2 Hz, 1H), 5.49 (d, J = 1.6 Hz, 1H), 7.21−7.53 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.90, 24.37, 27.52, 27.62, 39.00, 47.17, 58.52, 71.92, 72.68, 74.14, 77.24, 98.51, 127.61, 127.88, 128.28, 128.71, 128.79, 129.04, 137.37, 138.51, 169.35; GC/MS (NH_3) *m/z* 514 (MH)$^+$; $[\alpha]^{20}_D$ = −84.5° (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{27}H_{31}NO_5S_2$ 514.1715, found 514.1714.

***N*-[(1*S*,3*R*,4*S*,5*R*,8*S*,9*S*)-3,4,8,9-Tetraacetoxy-7-[[3′-(acetylthio)propyl]thio]-2-oxabicyclo[3.3.1]non-6-en-5-yl]-acetamide (18a).** Compound **17a** (22 mg, 53 μmol) was subjected to the standard acetolysis conditions at 0 °C and then warmed at rt for 12 h. Workup and chromatography on silica gel with 20% EtOAc/hexane gave **18a** (19 mg, 64%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 3H), 1.90−2.04 (m, 2H), 2.09 (s, 3H), 2.16 (s, 3H), 2.17 (s, 3H), 2.18 (s, 3H), 2.32 (s, 3H), 2.80 (t, J = 7.2 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 4.67 (dd, J = 1.9 Hz, J = 5.4 Hz, 1H), 5.10 (d, J = 7.8 Hz, 1H), 5.48 (dd, J = 1.0 Hz, J = 5.4 Hz, 1H), 5.69 (d, J = 1.9 Hz, 1H), 5.72 (bs, 1H), 6.03 (d, J = 7.8 Hz, 1H), 6.29 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.49, 20.85, 20.95, 23.72, 27.90, 28.11, 30.62, 30.83, 59.00, 68.78, 70.95, 71.02, 77.20, 89.58, 128.73, 133.62, 168.61, 169.76, 169.64, 170.18, 172.21, 195.62; GC/MS (NH_3) *m/z* 562 (MH)$^+$; HRMS calcd for $C_{23}H_{31}NO_{11}S_2$ 561.1338, found 561.1331.

***N*-[(1*S*,3*R*,4*S*,5*R*,8*S*,9*S*)-3,8-Diacetoxy-4,9-bis(benzyloxy)-7-[[3′-(acetylthio)propyl]thio]-2-oxabicyclo[3.3.1]non-6-en-5-yl]acetamide (18b).** Compound **17b** (21 mg, 41 μmol) was subjected to the standard acetolysis conditions at 0 °C for 0.5 h. Workup and chromatography 50% EtOAc/hexane gave **18b** (22 mg, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.86−1.92 (m, 2H), 2.13 (s, 3H), 2.18 (s, 3H), 2.30 (s, 3H), 2.73 (bt, J = 7.1 Hz, 2H), 2.94 (t, J = 7.1 Hz, 2H), 3.80 (d, J = 7.7 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 1.8 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 4.56−4.61 (m, 2H), 4.80 (d, J = 12.2 Hz, 1H), 5.04 (bs, 1H), 5.32 (dd, J = 1.2 Hz, J = 5.3 Hz, 1H), 5.58 (d, J = 1.2 Hz, 1H), 5.96 (d, J = 7.7 Hz, 1H), 7.16−7.47 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.66, 21.20, 23.50, 27.94, 30.60, 30.73, 59.72, 70.77, 71.94, 72.34, 74.13, 74.58, 75.07, 92.62, 127.46, 127.64, 128.27, 128.34, 128.52, 128.84, 128.99, 129.11, 129.17, 130.56, 133.05, 137.34, 137.87, 168.66, 169.60, 170.57, 195.57; GC/MS (NH_3) *m/z* 658 (MH)$^+$; HRMS calcd for $C_{33}H_{40}NO_9S_2$ 658.2144, found 658.2148.

***N*-[(1*R*,3*S*,4*S*,5*R*,9*S*)-4,9-Bis(benzyloxy)-7-formyl-3-[(*p*-methoxybenzyl)oxy]-2-oxabicyclo[3.3.1]non-7-en-5-yl]-acetamide (20b).** (Methoxymethyl)triphenylphosphonium chloride (1.78 g, 5.18 mmol) was suspended in anhydrous THF (50 mL) under argon, and *n*-BuLi (2.33 mL, 4.66 mmol, 2 M solution in hexane) was added, and the mixture was stirred for 1 h. Ketone **4** (549 mg, 1.3 mmol) was dissolved in anhydrous THF (5 mL) and was added to the red ylide solution. After 8 h the reaction was quenched by the addition of acetone, and the solution was concentrated and adsorbed onto silica gel. The mixture was filtered through a pad of silica gel using Et_2O as the eluent. The filtrate was concentrated, and the crude product was chromatographed on silica gel with 35−50% ethyl acetate/hexanes yielding the *E*- and *Z*-isomers **19** as 2:1 mixture (362 mg, 62%). This material (362 mg, 0.802 mmol) was dissolved in a 6:1 mixture of THF/1 N HCl (162 mL) and heated at 57 °C for 18 h. The solution was concentrated, dissolved in toluene, and evaporated to dryness. The residue was dissolved in saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried, filtered, and concentrated. The residue was purified on silica gel with 50% ethyl acetate/hexanes to give compound **20a** as a colorless syrup (335 mg, 95%). A portion of this material (204 mg, 0.466 mmol) was dissolved in dry THF (50 mL), and *p*-methoxybenzyl alcohol (1.74 mL, 14.0 mmol), molecular sieves (4 Å), and Amberlyst 15 ion-exchange resin were added. After 12 and 36 h the same amounts of the reagents were added again. Although starting material remained after 4 days, the reaction mixture was worked up by being filtered through a pad of silica gel and then concentrated. The residue was chromatographed on silica gel with 15, 25, 35, and 65% ethyl acetate/hexanes to give **20b** (162 mg, 62%) and **20a** (67 mg, 33%) as colorless syrups. For **20b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 3H), 2.89 (bs, 2H), 3.73 (d, J = 7.9 Hz, 1H), 3.81 (s, 3H), 4.50 (d, J = 11.1 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.57 (dd, J = 2.4 Hz, J = 6.4 Hz, 1H), 4.59 (d, J = 7.9 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 12.3 Hz, 1H), 4.72 (d, J = 2.4 Hz, 1H), 4.85 (d, J = 12.3 Hz, 1H), 4.87 (d, J = 11.1 Hz, 1H), 4.95 (s, 1H), 6.58 (d, J = 6.4 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 7.21−7.46 (m,

12H), 9.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.92, 27.41, 55.27, 57.68, 67.80, 71.25, 72.26, 73.99, 74.29, 77.24, 98.31, 113.81, 127.47, 127.53, 128.21, 128.57, 129.07, 129.19, 129.36, 129.69, 137.85, 138.47, 138.98, 144.22, 159.37, 169.82, 192.05; GC/MS (NH_3) *m/z* 558 $(MH)^+$; $[\alpha]^{20}_D = -93.2°$ (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{33}H_{35}NO_7$ 558.2482, found 558.2477.

***N*-[(1*R*,3*S*,4*S*,5*R*,9*S*)-4,9-Bis(benzyloxy)-7-(hydroxymethyl)-3-[(*p*-methoxybenzyl)oxy]-2-oxabicyclo[3.3.1]non-7-en-5-yl]acetamide (20c).** Compound **20b** (200 mg, 0.358 mmol) was dissolved in 2:1 EtOH/H_2O (32 mL), and $CeCl_3 \cdot 7H_2O$ (133 mg, 0.35 mmol) and $NaBH_4$ (20 mg, 0.53 mmol) were added at −10 °C. After 10 min the unreacted $NaBH_4$ was destroyed by the addition of acetone and the solution was concentrated. The residue was suspended in H_2O, and 1 N HCl was added until the solid dissolved. The solution was extracted with CH_2Cl_2 (3 × 15 mL), and the organic layer was dried, filtered, and concentrated. The residue was chromatographed on silica gel with 75% ethyl acetate/hexanes to give **20c** (175 mg, 87%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 3H), 2.57 (d, J = 18.6 Hz, 1H), 2.80 (d, J = 18.6 Hz, 1H), 3.70 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 4.03 (b, 2H), 4.40 (dd, J = 2.4 Hz, J = 6.4 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.51 (d, J = 11.3 Hz, 1H), 4.61 (d, J = 2.4 Hz, 1H), 4.66 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 12.3 Hz, 1H), 4.78 (d, J = 8.0 Hz, 1H), 4.85 (d, J = 12.3 Hz, 1H), 4.87 (d, J = 11.3 Hz, 1H), 4.95 (s, 1H), 5.68 (bd, J = 6.4 Hz, 1H), 6.88 (d, J = 9.4 Hz, 2H), 7.21−7.46 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.03, 31.05, 55.29, 58.22, 64.53, 68.07, 70.91, 71.85, 73.96, 75.20, 77.24, 97.84, 113.70, 115.50, 127.29, 127.45, 128.13, 128.66, 129.06, 129.21, 129.73, 129.83, 138.04, 138.79, 144.51, 159.25, 169.73; GC/MS (NH_3) *m/z* 560 $(MH)^+$; $[\alpha]^{20}_D = -93°$ (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{34}H_{37}NO_7$ 560.2638, found 560.2665.

***N*-[(1*R*,3*S*,5*R*,6*S*,8*S*,9*S*,10*S*)-9,10-Bis(benzyloxy)-3-(iodomethyl)-8-[(*p*-methoxybenzyl)oxy]-4,7-dioxatricyclo-[4.3.1.0^{3,5}]dec-1-yl]acetamide (21b).** Compound **20c** (74 mg, 132 μmol) was dissolved in dry CH_2Cl_2 (20 mL), and $NaHCO_3$ (80 mg, 0.9 mmol) and MCPBA (136 mg, 394 mmol) were added. The reaction mixture was worked up after 36 h by addition of $Na_2S_2O_3$/$NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried, filtered, and concentrated. The residue was chromatographed with 65% ethyl acetate/hexanes to give epoxide **21a** (56 mg, 74%). This material (39 mg, 67 μmol) was dissolved in dry toluene (9 mL). Triphenylphosphine (21 mg, 81 μmol), imidazole (11 mg, 162 μmol), and powdered iodine (19 mg, 74 μmol) were added, and the suspension was heated at 47 °C. After 5 h the same amount of the reagents was added. After a further 5 h, the solution was cooled and concentrated. The residue was chromatographed on silica gel with 100%−88% toluene/ethyl acetate to give compound **21b** (43 mg, 92%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (1, 3H), 2.69 (d, J = 15.7 Hz, 1H), 2.67 (d, J = 15.7 Hz, 1H), 3.06 (s, 2H), 3.24 (d, J = 3.2 Hz, 1H), 3.67 (d, J = 8.2, Hz, 1H), 3.81 (s, 3H), 4.49 (dd, J = 2.5 Hz, J = 3.2 Hz, 1H), 4.41 (d, J = 11.9 Hz, 1H), 4.55 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.68 (d, J = 2.5 Hz, 1H), 4.70 (d, J = 12.3 Hz, 1H), 4.83 (s, 1H), 4.90 (d, J = 12.3 Hz, 1H), 4.93 (d, J = 11.5 Hz, 1H), 5.12 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 7.5 Hz, 2H), 7.16−7.45 (m, 12H); GC/MS (NH_3) *m/z* 686 $(MH)^+$; HRMS calcd for $C_{33}H_{36}INO_7$ 686.1604, found 686.1608.

***N*-[(1*S*,3*S*,4*S*,5*R*,8*S*,9*S*)-4,9-Bis(benzyloxy)-8-hydroxy-3-[(*p*-methoxybenzyl)oxy]-7-methylene-2-oxabicyclo[3.3.1]-non-5-yl]acetamide (22a).** The iodo epoxide **21b** (43 mg, 0.062 mmol) was dissolved in 96% EtOH (10 mL). Activated zinc dust (41 mg, 0.63 mmol) was added, and the mixture was refluxed for 2 h. It was then cooled, filtered through a pad of silica gel, and concentrated. The residue was dissolved in H_2O (8 mL) and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel with 50% ethyl acetate/hexanes to give the title compound **22a** (33 mg, 96%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3H), 2.66 (d, J = 15.3 Hz, 1H), 3.38 (bd, J = 15.3 Hz, 1H), 3.70 (d, J = 7.8 Hz, 1H), 3.81 (s, 3H), 4.23 (dd, J = 2.0 Hz, J = 3.4 Hz, 1H), 4.39 (d, J = 3.4 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 12.2 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.80 (d, J = 12.2 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.93, (s, 1H), 5.00 (bs, 1H), 5.04 (d, J = 2.0 Hz, 1H), 5.14 (bs, 1H), 5.29 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 9.4 Hz, 2H), 7.20−7.44 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 24.11, 33.08, 55.28, 59.57, 70.43, 72.09, 72.74, 73.57, 74.24, 74.87, 97.58, 113.74, 117.37, 127.20, 127.32, 128.10, 128.50, 129.03, 129.19, 129.61, 129.93, 138.02, 138.93, 145.95, 159.30, 170.5; GC/MS (NH_3) *m/z* 560 $(MH)^+$, 422 (MH − PMBOH); $[\alpha]^{20}_D = -46.4°$ (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{33}H_{37}NO_7$ 560.2638, found 560.2624.

***N*-[(1*S*,3*S*,4*S*,5*R*,8*R*,9*S*)-4,9-Bis(benzyloxy)-8-(*tert*-butyldimethylsiloxy)-3-[(*p*-methoxybenzyl)oxy]-7-oxo-2-oxabicyclo[3.3.1]non-5-yl]acetamide (22c).** Compound **22a** (65 mg, 0.117 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Triethylamine (0.260 mL, 1.87 mmol), and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.213 mL, 0.935 mmol) were added, and the mixture was stirred for 8 h. The solution was extracted with aqueous saturated $NaHCO_3$ (7 mL), and the aqueous layer was twice extracted with 5 mL portions of CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The residue was chromatographed with 13−20% ethyl acetate/hexanes (linear gradient) to give **22b** (68 mg, 86%). A portion of this material (22 mg, 0.032 mmol) was dissolved in 1:1 CH_2Cl_2/MeOH (6 mL). Pyridine (33 μL, 0.040 mmol) was added, and after cooling to −78 °C, ozone was passed through the solution until the blue color persisted. After 15 min the solution was purged with argon, dimethyl sulfide (0.107 mL, 1.46 mmol) was added, and the mixture was warmed to rt for 30 min. The solution was concentrated, and the residue was dissolved in toluene and concentrated (2×). The crude was then chromatographed on silica gel with 15% ethyl acetate/hexanes to give the title compound **22c** (15 mg, 65%) as colorless crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.56 (s, 3H), 2.75 (dd, J = 1.6 Hz, J = 16.2 Hz, 1H), 3.73 (d, J = 7.7 Hz, 1H), 3.76 (d, J = 16.2 Hz, 1H), 3.84 (s, 3H), 3.99 (dd, J = 1.5 Hz, J = 3.4 Hz, 1H), 4.10 (dd, J = 2.1 Hz, J = 3.4 Hz, 1H), 4.43−4.69 (m, 5H), 4.84 (d, J = 12.4 Hz, 1H), 4.89 (d, J = 11.2 Hz, 1H), 4.96 (s, 1H), 5.25 (d, J = 2.1 Hz, 1H), 6.91 (d, J = 9.4 Hz, 2H), 7.26−7.49 (d, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.90, 23.91, 25.52, 40.54, 55.27, 58.87, 71.45, 71.80, 72.51, 73.75, 75.29, 75.37, 75.94, 76.16, 77.23, 98.62, 113.85, 127.51, 127.62, 128.24, 128.58, 129.06, 129.20, 129.79, 137.78, 138.38, 159.42, 170.05, 206.38; GC/MS (NH_3) *m/z* 676 $(MH)^+$; $[\alpha]^{20}_D = -29.4°$ (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{38}H_{49}NO_8Si$ 676.3220, found 676.3334.

***N*-[(1*S*,3*S*,5*R*,6*S*,7*R*,10*S*)-1,6,10-Triacetoxy-2,4-dioxatricyclo[3.3.1.1^{3,7}]dec-7-yl]acetamide (25b).** Samarium metal (174 mg, 1.16 mmol) was suspended in anhydrous degassed THF (11 mL). Diiodomethane (89 μL, 1.10 mmol) was added at 0 °C. After 15 min the solution was warmed to rt and stirred for 1 h. The dark blue solution was cooled to −78 °C, and ethylene glycol was added (146 μL, 2.6 mmol) followed by **4** (72 mg, 220 μmol) dissolved in 4 mL of anhydrous degassed THF. The solution was stirred at −78 °C for 10 min and then at rt for 30 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, and after usual workup the residue was adsorbed onto silica gel and chromatographed with 75−100% EtOAc/hexane (linear gradient) to yield **25a** (54 mg, 75%) as colorless crystals. The material was dissolved in pyridine (3 mL), Ac_2O (100 μL) was added, and the solution was stirred for 12 h. The mixture was concentrated, diluted with toluene, and evaporated (3×). The residue was purified on silica gel using 65% of EtOAc/hexane as the eluant to afford **25b** (61 mg) colorless crystals: mp 120 °C dec; ^{1}H NMR (300 MHz, C_6D_6) δ 1.49 (s, 3H), 1.52 (s, 3H), 1.60 (s, 3H), 1.70 (s, 3H), 1.79 (bd, J = 12.8 Hz, 1H), 2.53 (ddd, J = 3.5 Hz, J = 4.7, Hz, J = 12.8 Hz, 1H), 3.02 (d, J = 3.5 Hz, J = 12.6 Hz, 1H), 3.60 (d, J = 12.6 Hz, 1H), 4.26 (ddd, J = 1.0 Hz, J = 2.4 Hz, J = 4.7 Hz, 1H), 5.21 (m, 1H), 5.31 (d, J = 2.4 Hz, 1H), 6.06 (s, 1H), 6.14 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.99, 21.23, 22.03, 24.20, 35.29, 35.81, 56.69, 67.25, 70.53, 72.04, 94.86, 98.45, 168.05, 169.78, 170.09, 172.45; GC/CIMS (NH_3) *m/z* 389 $(M + NH_4)^+$, 372 $(MH)^+$; $[\alpha]^{20}_D = -43.5°$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_9$: C, 51.75; H, 5.70; N, 3.77. Found: C, 51.47; H, 5.74; N, 3.72.

***N*-[(1*S*,3*S*,5*R*,6*R*,7*S*,8*S*,10*S*)-5-Allyl-7,10-diacetoxy-4-oxo-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (26a).** To a solution of ketone **4** (19 mg, 0.058 mmol) in glacial acetic acid (1 mL) was added pyridinium bromide perbromide (26 mg, 0.064 mmol, tech. 80%). The reaction was heated at 70 °C for 4.5 h and then diluted with water (5 mL). The solution was extracted with CH_2Cl_2 (2 × 5 mL), and the organic layers were combined, washed with saturated aqueous $NaHCO_3$ (5 mL), dried, and concentrated. The residue was flash chromatographed with 60−80% ethyl acetate/petroleum ether (linear gradient) to yield the bromide (20 mg, 85%) as an inseparable mixture of α-bromo epimers: GC/MS (NH_3) *m*/*z* 423 $(M + NH_4)^+$. A benzene (5.2 mL) solution of this mixture (210 mg, 0.517 mmol), allyltributyltin (0.640 mL, 2.07 mmol), and AIBN (13 mg) was degassed with argon for 10 min. The reaction mixture was heated at 85 °C for 7.5 h, cooled, and concentrated. The residue was diluted with acetonitrile (20 mL) and extracted with hexanes (4 × 10 mL). The CH_3CN layer was concentrated, and the crude product was adsorbed onto silica gel. Flash chromatography with a linear gradient of 50−65% ethyl acetate/hexanes yielded an inseparable 4:1 mixture of **26a** (130 mg, 68%) and 8-*epi*-**26a**. For **26a**: colorless solid; mp 184−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 3H, Ac), 2.14 (s, 3H), 2.25 (s, 3H), 2.68 (m, 2H), 3.75 (dd, $J_1 = J_2 = 7.6$, 1H), 4.23 (d, $J = 6.1$, 1H), 5.01 (m, 1H), 5.03−5.07 (m, 2H), 5.17 (bs, 1H), 5.51 (d, $J = 1.5$, 1H), 5.56 (d, $J = 3.2$, 1H), 5.82 (m, 1H), 6.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.62, 21.18, 23.92, 34.78, 53.15, 60.10, 70.44, 73.17, 75.59, 79.21, 101.27, 116.06, 136.60, 169.35, 169.81, 172.45, 202.59; GC/MS (NH_3) *m*/*z* 345 $(M + NH_4)^+$, 328 $(MH)^+$. Anal. Calcd for $C_{24}H_{25}NO_6$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.45; H, 5.80; N, 3.78.

***N*-[(1*S*,3*S*,5*R*,6*R*,7*S*,8*S*,10*S*)-5-Allyl-7,10-bis(benzyloxy)-4-oxo-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (26b).**[32] Ketone **26a** (10.7 mg, 29 μmol) was dissolved in dry methanol (1 mL), and NaH (0.5 mg of 60% dispersion in mineral oil) was added. After 10 min the reaction mixture was neutralized with Amberlite IRC-50S ion-exchange resin and filtered, and the resin was rinsed with methanol and concentrated. The crude diol was diluted with THF (1 mL) and DMF (0.2 mL), and sodium hydride (3.6 mg of 60% dispersion in mineral oil, 90 μmol) was added. After 10 min, benzyl bromide (7.5 μL, 64 μmol) and tetrabutylammonium iodide (0.5 mg) were added. The reaction was quenched after 24 h by the addition of saturated aqueous NH_4Cl (3 mL), and the solution was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried and concentrated. The residue was chromatographed with 20−60% ethyl acetate/petroleum ether to give crude **26b** (4.4 mg). A pure sample could be obtained by HPLC: mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.66 (m, 1H), 2.89 (m, 1H), 3.40 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 1H), 3.82, (s, 1H), 4.1 (dd, $J = 6.1$ Hz, 1H), 4.32−4.38 (m, 2H), 4.55−4.62 (m, 3H), 4.87 (d, $J = 12.3$ Hz, 1H), 4.96−5.06 (m, 3H), 5.67 (s, 1H), 5.83 (m, 1H), 7.24−7.49 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.86, 35.56, 53.89, 60.66, 72.47, 72.82, 74.11, 76.24, 79.44, 80.57, 100.72, 115.80, 127.80, 127.87, 128.41, 128.76, 128.93, 129.20, 136.93, 137.64, 137.89, 167.71, 205.15; GC/MS (NH_3) *m*/*z* 464 $(MH)^+$; $[\alpha]^{20}_D = -51.9°$ (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{27}H_{29}NO_6$ 464.2065, found 464.2061.

***N*-[(1*S*,3*S*,4*S*,5*R*,6*R*,7*S*,8*S*,10*S*)-5-Allyl-7,10-bis(benzyloxy)-4-iodo-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-6-yl]acetamide (27b).** Ketone **26b** (143 mg, 0.308 mmol) was dissolved in EtOH (15 mL), and $NaBH_4$ (45 mg, 1.23 mmol) was added at 0 °C. After 15 min the unreacted $NaBH_4$ was destroyed by the addition of acetone. The solution was concentrated, dissolved in H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel with a linear gradient of 40−50% ethyl acetate/hexanes to give **27a** (23 mg, 86%) as a colorless syrup. This alcohol (152 mg, 0.326 mmol) was dissolved in toluene (10 mL), and triphenylphosphine (162 mg, 0.73 mmol), imidazole (86 mg, 1.46 mmol), and powdered iodine (144 mg, 0.56 mmol) were added. The mixture was warmed to 95 °C for 50 min, cooled, and concentrated. The residue was adsorbed onto silica gel and filtered through a pad of silica gel with Et_2O. The solvent was concentrated, and the residue was chromatographed on silica gel with 20% ethyl acetate/hexanes to give **27b** as a colorless syrup (179 g, 89%): ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 2.37 (ddd, $J = 9.8$ Hz, $J = 12.0$ Hz, $J = 14.5$ Hz, 1H), 2.64 (bd, $J = 14.5$ Hz, 1H), 3.49 (dd, $J = 3.1$ Hz, $J = 12.0$ Hz, 1H), 3.77 (bs, 1H), 4.25 (d, $J = 12.4$ Hz, 1H), 4.33 (bd, $J = 3.3$ Hz, 1H), 4.48 (dd, $J = 3.1$ Hz, $J = 5.7$ Hz, 1H), 4.54 (dd, $J = 3.3$ Hz, $J = 5.7$ Hz, 1H), 4.60 (d, $J = 11.3$ Hz, 1H), 4.65 (d, $J = 11.3$ Hz, 1H), 4.81 (d, $J = 12.4$ Hz, 1H), 4.91 (s, 1H), 5.08−5.20 (m, 2H), 5.40 (d, $J = 3.1$ Hz, 1H), 5.42 (bs, 1H), 5.72 (dddd, 1H), 7.24−7.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.44, 24.10, 38.91, 48.50, 62.10, 72.39, 72.58, 72.60, 74.06 80.42, 82.42, 99.26, 117.67, 127.72, 128.06, 128.34, 128.55, 128.76, 129.15, 137.09, 137.29, 138.33, 169.48; GC/MS (NH_3) *m*/*z* 576 $(MH)^+$; $[\alpha]^{20}_D = -165.3°$ (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{27}H_{30}INO_5$ 576.1238, found 576.1233.

Methyl [(1*S*,3*S*,4*S*,5*R*,6*R*,7*S*,8*S*,10*S*)-6-Acetamido-7,10-bis(benzyloxy)-4-iodo-2,9-dioxatricyclo[4.3.1.0^{3,8}]dec-5-yl]-acetate (28a). Alkene **27b** (179 mg, 0.137 mmol) was dissolved in 5:1 CH_2Cl_2/MeOH (9.6 mL) and cooled to −78 °C. Ozone was bubbled through the solution until the blue color persisted. The solution was purged with argon, warmed to room temperature, and concentrated. The residue was dissolved in toluene and concentrated (4×). The resulting crude hydroperoxide was carefully dissolved in dry CH_2Cl_2 (7 mL), and Ac_2O (64 μL, 0.686 mmol) and Et_3N (143 μL, 1.03 mmol) were added. The mixture was stirred for 3 h and then extracted with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic layers were dried, filtered, and concentrated. Chromatography on silica gel with 30% ethyl acetate/hexanes yielded **28a** and the aldehyde **28b** as an inseparable mixture (77 mg). In order to isolate the pure methyl ester the mixture was dissolved in benzene (10 mL), and PPTS (17 mg, 67 μmol) and ethylene glycol (0.150 mL, 2.67 mmol) were added. After 1 h at reflux the solution was cooled and concentrated. The residue was dissolved in saturated aqueous $NaHCO_3$, and the solution was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were dried, filtered, and concentrated. The residue was dissolved in toluene, concentrated again, and then chromatographed on silica gel with 25−50% ethyl acetate/hexanes (linear gradient). The desired ester **28a** was obtained as a colorless syrup (57 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 2.75−2.90 (m, 2H), 3.71 (s, 3H), 3.76 (bs, 1H), 3.38 (dd, $J = 4.7$ Hz, $J = 10.2$ Hz, 1H), 4.25 (d, $J = 12.8$ Hz, 1H), 4.34 (dd, $J = 0.9$ Hz, $J = 3.3$ Hz, 1H), 4.46−4.55 (m, 2H), 4.59 (d, $J = 11.4$ Hz, 1H), 4.65 (d, $J = 11.4$ Hz, 1H), 4.79 (d, $J = 12.3$ Hz, 1H), 4.84 (s, 1H), 5.42 (d, $J = 1.2$ Hz, 1H), 5.48 (d, $J = 3.1$ Hz, 1H), 7.26−7.48 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.21, 24.05, 38.85, 45.48, 51.81, 61.52, 71.97, 72.42, 72.66, 73.99, 80.43, 82.10, 99.28, 127.76, 128.05, 128.35, 128.63, 128.87, 129.21, 137.08, 138.23, 169.56, 173.15; GC/MS (NH_3) *m*/*z* 608 $(MH)^+$; $[\alpha]^{20}_D = -141.6°$ (*c* 0.5, $CHCl_3$); HRMS calcd for $C_{27}H_{30}INO_7$ 608.1136, found 608.1150.

(1*R*,3*S*,4*S*,5*R*,6*S*,9*S*)-5-Acetamido-4,9-bis(benzyloxy)-3-[(*p*-methoxybenzyl)oxy]-2-oxabicyclo[3.3.1]non-7-en-6-yl]-acetic Acid (29c). To a solution of **28a** (63 mg, 0.104 mmol), in anhydrous EtOH (8 mL), was added freshly activated zinc dust (103 mg, 1.56 mmol). This mixture was refluxed for 2 h, filtered through a bed of silica gel, and concentrated. The residue was dissolved in H_2O (8 mL) and extracted with CH_2Cl_2 (3 × 8 mL) The combined organic layers where dried, filtered, and concentrated. The residue was chromatographed on silica gel with 35−40% ethyl acetate/hexanes to give **29a** (48 mg, 82%) as a colorless syrup. This material was dissolved in anhydrous DMF (9 mL), and silver(I) oxide (300 mg, 1.26 mmol), tetrabutylammonium iodide (72 mg, 1.88 mmol), and 4-methoxybenzyl chloride (1.4 mL, 1.56 mmol) were added. After 12 h the mixture filtered through a pad of silica gel. The filtrate was concentrated, diluted with EtOAc, and filtered through a bed of silica gel again. The crude product was

(32) A better yielding preparation is being developed which will be described subsequently.

chromatographed on silica gel with a linear gradient of 25−50% ethyl acetate/hexanes to afford **29b** (54 mg, 92%) as a colorless oil. A portion (46 mg, 77 μmol) was dissolved in 3:1 MeOH/H_2O (4.8 mL). Lithium hydroxide (64 mg, 1.53 mmol) was added at 0 °C, and the reaction kept at this temperature for 6 h. The solution was concentrated, dissolved in 1 N HCl (6 mL), and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel with 50−100% acetone/hexanes to give **29c** (44 mg, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 2.46 (dd, J = 10.9 Hz, J = 16.4 Hz, 1H), 2.85 (dd, J = 4.2 Hz, J = 16.4 Hz, 1H), 3.80−3.88 (m, 2H), 3.81 (s, 3H), 4.40 (dd, J = 2.0 Hz, J = 5.9 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.71 (bs, 1H), 4.83 (d, J = 12.5 Hz, 1H), 4.88 (s, 1H), 4.88 (d, J = 11.6 Hz, 1H), 4.99 (d, J = 8.3 Hz, 1H), 5.62 (ddd, J = 7.6 Hz, J = 5.9 Hz, J = 9.6 Hz, 1H), 5.93 (dd, J = 1.8 Hz, J = 9.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.16−7.48 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.90, 35.02, 39.72, 55.28, 61.00, 68.43, 71.12, 71.88, 74.51, 75.98, 78.61, 97.68, 113.76, 120.70, 127.21, 128.69, 129.21, 129.54, 129.76, 135.72, 138.78, 138.80, 159.23, 170.22, 177.70; GC/MS (NH_3) m/z 588 $(MH)^+$, 450 $(MH - PMBOH)^+$; $[\alpha]^{20}_D$ = −56.1° (c 0.5, $CHCl_3$); HRMS calcd for $C_{34}H_{37}NO_8$ 588.2587, found 588.2601.

***N*-[(1*R*,2*R*,6*R*,7*R*,8*S*,10*S*,11*S*,12*S*)-11,12-Bis(benzyloxy)-7-iodo-10-[(*p*-methoxybenxyl)oxy]-4-oxo-5,9-dioxatricyclo-[6.3.1.0^{2,6}]dodec-1-yl]acetamide (32a).** To compound **29c** (12.7 mg, 21.6 μmol), in dry CH_3CN (2.5 mL), was added iodonium dicollidine perchlorate (15.2 mg, 32.4 μmol), and the mixture was stirred in the dark for 4 h. It was then concentrated, dissolved in aqueous $Na_2S_2O_3$ (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel with 25−75% ethyl acetate/hexanes (linear gradient) to give the title compound **32a** (13.2 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.42 (dd, J = 9.3 Hz, J = 17.7 Hz, 1H), 3.10 (dd, J = 17.7 Hz, 1H), 3.76 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 4.01 (dd, J = 6.2 Hz, J = 9.1 Hz, 1H), 4.46−4.54 (m, 3H), 4.57−4.63 (m, 2H), 4.71 (d, J = 1.4 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.83−4.90 (m, 2H), 5.02 (d, 6.2 Hz, 1H), 5.20 (d, J = 8.0 Hz, 1H), 5.22 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 7.23−7.48 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.30, 24.01, 33.15, 39.07, 55.30, 58.01, 71.23, 71.56, 72.01, 74.25, 76.96, 83.54, 99.04, 113.86, 127.55, 128.24, 128.85, 129.27, 129.45, 129.75, 137.40, 138.01, 159.36, 170.03, 175.02; GC/MS (NH_3) m/z 731 $(M + NH_4)^+$, 714 $(MH)^+$, 576 $(MH - PMBOH)^+$; $[\alpha]^{20}_D$ = −44° (c 0.5, $CHCl_3$); HRMS calcd for $C_{34}H_{36}INO_8$ 714.1553, found 714.1566.

***N*-[(1*R*,2*R*,6*R*,7*R*,8*R*,10*S*,11*S*,12*S*)-11,12-Bis(benzyloxy)-7-hydroxy-10-[(*p*-methoxybenxyl)oxy]-4-oxo-5,9-dioxatricyclo[6.3.1.0^{2,6}]dodec-1-yl]acetamide (32b).** Iodide **32a** (10.5 mg, 14.7 μmol) was dissolved in anhydrous toluene (1.5 mL). Oxygen was bubbled into the solution for 10 min, and then Bu_3SnH (10 μL, 36.8 μmol) and Et_3B (29 μL of a 0.1 M solution in toluene) were added while the bubbling of oxygen was continued. Further amounts of Et_3B (29 μL of a 0.1 M solution in toluene) and Bu_3SnH (10 μL, 36.8 μmol) were added after 2.75, 4.25, and 36 h. After a further 10 h the solution was concentrated. The residue was dissolved in acetonitrile (5 mL) and extracted with hexanes (3 × 5 mL). The acetonitrile layer was concentrated, and the residue was chromatographed on silica gel with a linear gradient of 35−65% ethyl acetate/hexanes to give unreacted **32a** (8.1 mg) and **32b** (1.0 mg, 11%) as a colorless syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.45 (dd, J = 9.5 Hz, J = 17.8 Hz, 1H), 3.12 (d, J = 17.8 Hz, 1H), 3.73 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 3.82−3.91 (m, 1H), 4.08 (bs, 1H), 4.34 (bs, 1H), 4.46−4.66 (m, 5H), 4.70 (d, J = 2.1 Hz, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.86 (bs, 1H), 4.87 (d, J = 11.2 Hz, 1H), 5.02 (d, J = 8.0 Hz, 1H, H1), 5.30 (s, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.20−7.45 (m, 12H); GC/MS (NH_3) m/z 604 $(MH)^+$, 446 $(MH - PMBOH)^+$; HRMS calcd for $C_{34}H_{37}NO_9$ 604.2536, found 604.2556.

Supporting Information Available: Experimental procedures for **23** and **34** along with characterization data for **19**, **20a**, **21a**, **22b**, **23**, **25a**, **27a**, **28b**, **29a**, **29b**, **30**, **31**, and **34** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951747O