# Free Radical Macrocyclizations from Steroid-Derived Precursors

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Stereoselective free radical addition reactions were studied using steroid-derived templates in an attempt to control product dispersity. Templates were prepared from bifunctional steroids appropriately substituted with initiating and terminating functionality. Free radical initiation in the presence of a polymerizable olefin resulted in the formation of macrocycles that had incorporated monomer. The yield of macrocycle formed was as high as 51% for templates derived from lithocholic acid whereas templates derived from androstanolone failed to give significant amounts of macrocycles. The effects of variation of initiating and terminating functionality, steroid, and olefin on macrocycle size and yield were examined.

An enormous amount of research performed over the last 10 years involves the use of rigid organic template molecules to impart selectivity to chemical transformations.[1,2] These approaches typically involve the imposition of a regio- or stereochemical preference on an exogenous reagent by the steric bulk and/or geometry of a template either covalently attached[1] or transiently bound[2] to the substrate. As applied to polymerization reactions, the term template has typically meant a polymeric substance which serves to preorient monomer units.[3] One of the most thoroughly studied examples of this strategy is the polymerization of styrenesulfonate along an ionene template.[4] Electrostatic attraction between the monomers and the ionene bring monomers into a linear arrangement prior to polymerization. The result of this preorganization is significant rate enhancement of polymerization. Similar approaches have been employed by covalently binding several monomer units to a template. Wulff used this strategy to impose stereoselection and monomer sequence in a process which he dubbed "cyclocopolymerization".[5] A similar strategy has been used by Kammerer to control oligomer dispersity.[6] While covalently or electrostatically binding a monomer to a polymeric template does provide a means for obtaining oligoselectivity, there are practical disadvantages to these strategies. For example, the template itself is an oligomeric compound, and its preparation must be either by an iterative synthesis or by a polydisperse oligomerization reaction with subsequent separation of the template.

Another approach to control oligomer size, pioneered by Feldmann,[7,8] makes use of a rigid template whose sole purpose is to separate initiating and terminating groups. As applied to oligomerization reactions, this approach entails substitution of one end of the template with a group that could initiate free radical polymerization and substitution at a fixed distance away from some terminating or chain-transfer group. This approach is presented in Figure 1. Free radical formation at the initiator is followed by addition of olefin monomer. Successive additions occur until the intermediate polymer free radical is within a reactive distance of the terminator. At this point, the effective concentration of the tethered terminator relative to the growing oligomer free radical will be much higher than its actual concentration in solution. By this method, the last step is simply a free radical macrocyclization, a process with good precedent.[9] The size of the oligomer formed before macrocyclization is presumably dependent on the size of the gap between the initiator and terminator, with the result being *oligoselectivity*.[8] To serve simply as a template, the rigid spacer would be connected to the oligomer chain via cleavable junctions, allowing removal of the oligomer as a synthetically useful fragment. This approach was used by Feldman to produce an $n = 3$ oligomer of methyl methacrylate with a polynorbornadiene spacer, trichloroacetate/$Mo(CO)_6$ initiator, and $\alpha$-(phen-

(1) For examples, see: (a) Oppolzer, W.; Loher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2808. (b) Seebach, D.; Imwinkelreid, R.; Weber, T. *Modern Synth. Methods* **1983**, *4*, 128. (c) Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 1. (d) Lutomski, K. A.; Meyers, A. I. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 218. (e) Enders, D. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 275. (f) Whitesell, J. K.; Bhatacharya, A.; Buchanan, C. M.; Chen, H. H.; Devo, D.; James, D.; Liu, C.-L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993. (g) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296 and references cited therein.

(2) For examples, see: (a) Mazaleyrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. (c) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5. (d) Masamune, S.; Sato, T.; Kim, B. M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (e) Kitimura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (f) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510. (g) Rebek, J.; Marshall, L.; McManis, J.; Wolak, R. *J. Org. Chem.* **1986**, *51*, 1649. (h) Breslow, R. *Chemtracts Org. Chem.* **1988**, *1*, 333. (i) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (j) Groves, J. T.; Neumann, R. *J. Org. Chem.* **1988**, *53*, 3891 and references cited therein.

(3) Tan, Y. Y. In *Recent Advances in Mechanistic and Synthetic Aspects of Polymerization*; Fontanille, M., Guyot, A., Eds.; D. Reidel: Boston, 1987; p 281 and references cited therein.

(4) (a) Blumstein, A.; Kakivaya, S. R.; Shah, K. R.; Wilkins, D. H. *J. Polym. Sci.* **1974**, *45*, 75. (b) Blumstein, A.; Kakivaya, S. R. *Polymerization of Organized Systems*; Elias, H. G., Ed.; Gordon and Breach: London, 1977; p 189. (c) Blumstein, A.; Weill, G. *Macromolecules* **1977**, *10*, 75.

(5) Wulff, G. In *Recent Advances in Mechanistic and Synthetic Aspects of Polymerization*; Fontanille, M.; Guyot, A., Eds.; D. Reidel: Boston, 1987; p 399.

(6) (a) Kammerer, H.; Shukla, J. S. *Makromol. Chem.* **1968**, *116*, 62. (b) Kamerer, H.; Steiner, V.; Gueniffey, H.; Pinazzi, C. P. *Makromol. Chem.* **1976**, *177*, 1665. (c) Kammerer, H.; Hegemann, G.; Onder, N. *Makromol. Chem.* **1982**, *183*, 1435. (d) Kammerer, H.; Hegemann, G. *Makromol. Chem.* **1984**, *185*, 635. (e) Miracle, G. S.; Cannizzaro, S. M.; Porter, N. A. *J. Am. Chem. Soc.* **1992**, *114*, 9683.

(7) Feldman, K. S.; Lee, Y. B. *J. Am. Chem. Soc.* **1987**, *109*, 5850.

(8) Feldman, K. S.; Bobo, J. S.; Ensel, S. M.; Lee, Y. B.; Weinreb, P. H. *J. Org. Chem.* **1990**, *55*, 474.

(9) (a) Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787. (b) Porter, N. A.; Chang, V. H.-T. *J. Am. Chem. Soc.* **1987**, *109*, 4976. (c) Porter, N. A.; Chang, V. H.-T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554. (d) Porter, N. A. Stereochemical and Regiochemical Aspects of Free Radical Macrocyclizations. *Organic Free Radicals*; Proceedings of the Fifth International Symposium; Fischer, H., Heimgartner, H., Eds.; Springer-Verlag; Berlin, 1988, p 187. (e) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309.

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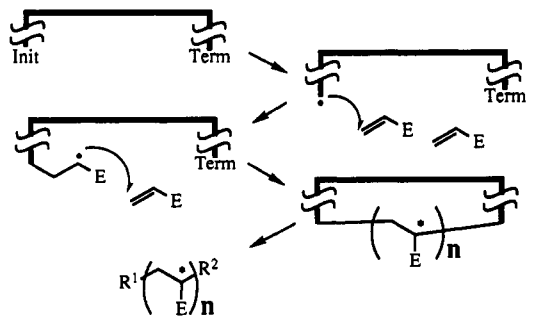



**Figure 1.** Idealized free radical oligomerization template.

ylthio)methacrylate terminator.[7,8] The macrocycle was obtained in 41% yield. Although methyl methacrylate produces atactic polymers, only six of the eight possible stereoisomers were detected in a 5:5:19:9:8:54 ratio.

Recent developments in the control of stereoselectivity in radical additions allow control of tacticity in simple telomerization reactions.[10] Chiral pyrrolidines, oxazolidines, and sultams attached via an amide linkage to a prostereogenic radical center exert diastereofacial selectivity in the addition reactions of the radical.[11] The use of auxiliary groups to control stereoselectivity along with templates to control oligoselectivity would provide an entry into complex compounds with iterative substructures that would otherwise be difficult to prepare. We report here our use of steroid templates coupled to chiral acrylamide olefins with the goal of achieving stereoselective and oligoselective iterative radical additions.

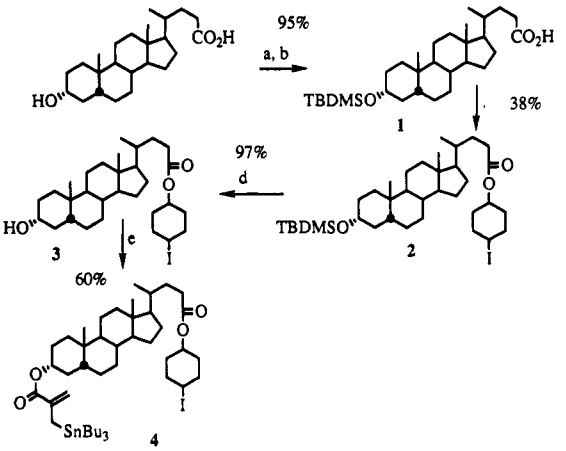
## Results

We initially chose the bifunctional steroid, lithocholic acid, as a starting material for free radical oligomerization templates. This compound contains different functional groups at opposite ends of the molecule, allowing for a straightforward synthesis. It is also commercially available and inexpensive. The target template was chosen to have tin methacrylate substitution at the 3-position of the steroid and an iodide attached to the side chain.

The iodocyclohexyl lithiocholate template 4 was prepared according to Scheme I. The 3-OTBDMS lithocholic acid 1 was formed by first diprotecting, then cleaving the silyl ester.[12] The carboxylic acid was then esterified by reaction with dicyclohexylcarbodiimide, *trans*-4-iodocyclohexanol, and (dimethylamino)pyridine. Iodocyclohexanol was prepared by opening oxabicycloheptane with 47% HI.[13] The silyl ether 2 was then deprotected with HF in acetonitrile to the sterol 3 which was acylated with α-(tributylstannyl)methacryloyl chloride[14] and pyridine, yielding the template 4.

The iodocyclohexyl template was reacted with either pyrrolidine 5, 2,5-dimethylpyrrolidine 6, or phenyloxazolidine acrylamides 7, with either photolytic initiation by hexabutylditin and a 250-W sun lamp or with initiation

**Scheme I.[a] Synthesis of Iodocyclohexyl Lithocholate Template, 4**




[a] TBDMSCl, imidazole; (b) $K_2CO_3$, MeOH/THF/$H_2O$; (c) *trans*-4-iodocyclohexanol, DCC, DMAP; (d) HF, $CH_3CN$; (e) α-(tributylstannyl)methacryloyl chloride, pyridine.

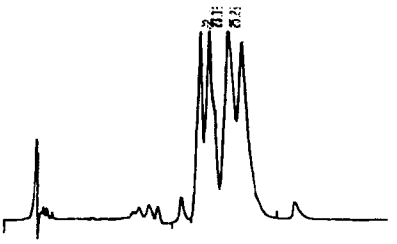
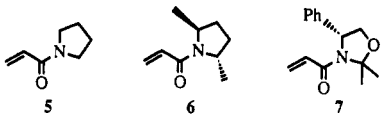


**Figure 2.** Normal-phase analytical HPLC chromatogram of the $n = 1$ macrocycles from the reaction of iodocyclohexyl template 4 with pyrrolidine acrylamide.

by triethylborane in the presence of atmospheric oxygen.[15] The anticipated products of this reaction, 8, are macrocycles that include the acrylamide in the ring structure.




Because of the small distance between initiator and terminator, the $n = 1$ macrocycles predominanted in the product mixture, as evidenced by mass spectrometric analysis. In addition to macrocycles, all reactions produced polymeric material which did not elute through silica. The $n = 1$ macrocyclic product, 8a, was isolated by preparative normal-phase HPLC. Systematic variation of template and olefin concentration produced a 51% yield of this product when initial template concentration was 1.0 mM and initial olefin concentration was 25 mM. The macrocyclic product thus obtained was shown to be a mixture of all four possible diastereomers by analytical normal-phase HPLC. Figure 2 shows the chromatogram containing the diastereomeric products 8a.

The macrocyclization procedures were repeated with 2(*S*),5(*S*)-dimethylpyrrolidine acrylamide 6 in the same concentrations as outlined above. After reaction, most of the acylamide (73%) was removed by Kugelrohr distillation (80 °C/50 μ). The macrocycle was then isolated from the product mixture by preparative normal-phase HPLC in 29% yield. Analytical separation by normal- and reverse-phase HPLC showed this product to consist

(10) (a) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. (b) Porter, N. A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T.; McPhail, A. T. *J. Am. Chem. Soc.* **1991**, *113*, 7002.

(11) Porter, N. A.; Bruhnke, J. D.; Wu, W.-X.; Rosenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788.

(12) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102.

(13) Takeoka, Y. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1371.

(14) (a) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339–1340. (b) Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B.; Robertson, J. *Tetrahedron* **1991**, *47*, 5901–5918.

(15) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143–147.

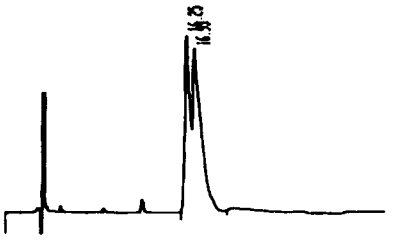
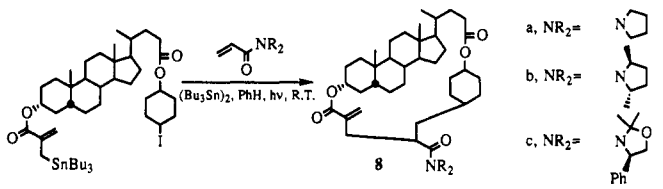


**Figure 3.** Normal-phase analytical HPLC chromatogram of the $n$ = 1 macrocycles, **8b**, from the reaction of iodocyclohexyl template **4** with 2(*S*),5(*S*)-dimethylpyrrolidine acrylamide.

**Scheme II. Macrocyclization of Iodocyclohexyl Template, 4**




of two components, presumably due to stereorandom addition of the cyclohexyl radical to the acrylamide followed by stereoselective addition of the amide-substituted radical to the allylstannane. The normal-phase analytical HPLC chromatogram is shown in Figure 3. One of the diastereomeric $n$ = 1 macrocycles, **8b**, was collected by analytical reverse-phase HPLC, producing a crystalline solid. Unfortunately, the crystals proved to be unsuitable for X-ray structure analysis.

In an attempt to detect larger macrocycles, the crude product mixture was subjected to chemical ionization mass spectral examination. This analysis showed trace amounts of the $n$ = 2 and $n$ = 3 macrocycles. Because of the unknown efficiency of the interface with high molecular weight substrates, and because of the unknown response factors, these data cannot be taken as an accurate quantitative indication of macrocycle size distribution. Nevertheless, it is clear that some larger macrocycles are formed.

In an attempt to obtain a crystalline sample of a macrocycle suitable for X-ray structure analysis, and to investigate the reaction of the iodocyclohexyl template **4** with one of the oxazolidine-substituted acrylamides, template **4** was reacted with the phenyloxazolidine acrylamide **7**. With the initial template concentration at 1.0 mM, the olefin concentration at 20 mM, and catalytic hexabutylditin, the benzene solution was irradiated with a medium-pressure mercury lamp through Pyrex. After complete consumption of **4**, most of the unreacted olefin was removed by crystallization. The $n$ = 1 macrocycles were then isolated by normal-phase preparative HPLC in 31% yield. The diastereomers were inseparable by HPLC; however, NMR showed two major isomers in a 1.9:1 ratio. Repeated fractional crystallization from dichloromethane/methanol allowed isolation of the major isomer as a crystalline solid which was subjected to X-ray analysis. The structure of the major stereoisomer of macrocycle **8c** in crystals of the methanol solvate is shown in Figure 4.

**Iodopropyl and Iodoacetate Templates.** In an effort to increase the initiator/terminator gap size, two different lithocholic acid based templates were prepared. The first of these substrates, **9**, was structurally similar to **4** but had an iodopropyl initiator group. The other species, **10**, was an iodoacetate of the alcohol resulting from reduction of lithocholic acid. The iodopropyl template **9** was prepared

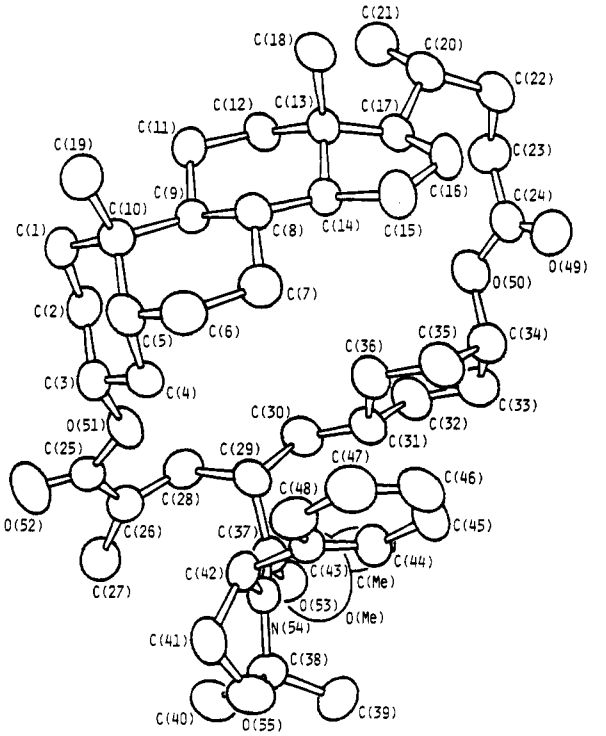
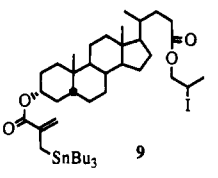
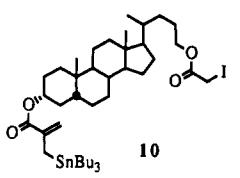



**Figure 4.** ORTEP diagram showing the atom numbering scheme and solid-state conformation of the major stereoisomer of macrocycle (**8c**) in crystals of the methanol solvate; hydrogen atoms have been omitted for clarity.

by a scheme analogous to that used to prepare **4**. The TBDMS-protected lithocholic acid **1** was reacted with 2-iodo-1-propanol[16] and DCC to produce the iodopropyl ester. Deprotection of the sterol and acylation of the 3-hydroxy group with (tributylstannyl)methacryloyl chloride produced the template. The iodoacetate template **10** was prepared starting also from **1**. The TBDMS-protected lithocholic acid **1** was reduced with borane to the alcohol[17] which was converted to an iodoacetate by reaction with iodoacetic acid and DCC. The TBDMS group was then removed, producing a sterol which was acylated with (tributylstannyl)methacryloyl chloride to yield the iodoacetate template **10**.




**9**

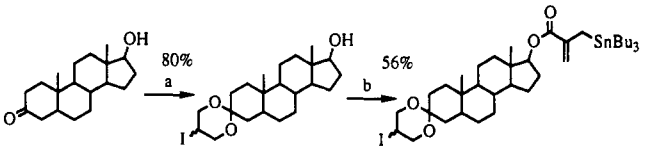



**10**

Iodopropyl template **9** (1.0 mM) was reacted with pyrrolidine acrylamide **5** (25 mM) in benzene in a water-jacketed flask. Initiation was performed by photolysis with hexabutylditin. The product mixture was separated by reverse-phase preparative HPLC after removal of polymeric material by silica gel filtration. The products were analyzed by reverse-phase analytical HPLC/mass spectrometry with a thermospray interface and chemical ionization with methane and ammonia. The mass spectrum of the unseparated mixture shows all macrocycles up to $n$ = 4 ($m/z$ M + H$^+$ 986), the mass limit of the spectrometer being $m/z$ 1000; the greatest intensity was

(16) Ficket, W.; Garner, H. K.; Lucas, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 5063.
(17) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stock, T. P. *J. Org. Chem.* **1973**, 2786–2792.

**Scheme III.[a] Synthesis of Iodoacetal Templates 12(α) and 12(β)**




[a] 2-Iodo-1,3-propanediol, TsOH, PhH, $-H_2O$; (b) α-(tributylstannyl)methacryloyl chloride, pyridine.

displayed for $n = 2$. Although the chromatograms show poor separation, and the efficiency of the interface becomes suspect for the higher mass products, it is readily seen that there must be numerous isomers for each size of macrocycle. Most instructive is the chromatogram for the $n = 2$ macrocycle. This is comprised of a minimum of seven chromatographic peaks. With three uncontrolled stereocenters, this macrocycle would be expected to be a mixture of eight stereoisomers.

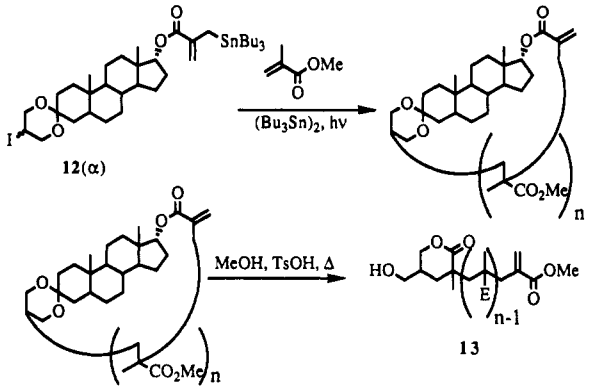
When the same reaction was performed with 2(*S*),5-(*S*)-dimethylpyrrolidine acrylamide **6**, the product analysis displayed a simplified mixture of macrocycles. Reaction, workup, and analysis were performed as they were for the reaction of **9** with the achiral olefin, except that the majority of unreacted olefin was removed by Kugelrohr distillation. The mass spectrum of the unseparated product mixture showed all size macrocycles up to the mass limit of the spectrometer, in this case $n = 1$, $n = 2$, and $n = 3$. Peak intensities were similar for all three products. The HPLC/mass chromatograms show that for the $n = 1$ and $n = 2$ macrocycles, the chromatograms both appear as two major peaks with other unresolved minor peaks. For the $n = 3$ macrocycles the chromatogram is poorly resolved, presumably due to inefficiency of the interface.

The iodoacetate template **10** was reacted with pyrrolidine acrylamide **5** by the photolytic ditin procedure used previously. Workup and analysis as before produced evidence for only trace amounts of the macrocyclic products. The mass spectrum of the unseparated product mixture shows macrocycles up to $n = 4$, with the signal from $n = 2$ having the greatest intensity. The HPLC/mass chromatograms show some simplification because the acetate does not produce a stereogenic center in addition to those of the spanning oligomer. Accordingly, the $n = 1$ macrocycle appears as two isomeric products, and the $n = 2$ homolog appears as four isomeric products. The two higher sized macrocycles are poorly resolved. Because of the very low yields of macrocyclic products, the iodoacetate was not studied further.

**Androstanolone Iodoacetal Templates.** In an effort to increase the size of the initiator–terminator gap and to increase the rigidity of the spacer, attention was turned to androstanolone-derived templates. A pair of templates derived from the 17α and 17β epimeric sterols was targeted for study. Androstanolone is commercially available as the 17β-hydroxy isomer; however, the 17α-hydroxy epimer was readily produced in large scale, using Mitsunobu esterification conditions (DEAD, $Ph_3P$). Hydrolysis yields pure 17α-hydroxyandrostanolone.

The templates were synthesized in two steps from either androstanolone epimer as shown in Scheme III. Reaction of either 17α- or 17β-androstanolone with 2-iodo-1,3-propanediol yielded acetal **11**, designated **11(α)** or **11(β)** depending on stereochemistry at the 17-position. Reaction of **11** with (tributylstannyl)methacryloyl chloride yielded

**Scheme IV. Reaction of Iodoacetal Template 12(α) with Methyl Methacrylate**




the two templates **12(α)** and **12(β)**. The full synthesis of the iodo diol was accomplished in the following manner. Benzaldehyde was reacted with glycerol forming a mixture of all four possible acetal isomers. *cis*-2-Phenyl-5-hydroxy-1,3-dioxane was separated from the mixture by repeated fractional crystallization.[18] Conversion to the tosylate followed by reaction with sodium iodide in DMF yielded 5-iododioxane. Hydrogenolysis of the benzylidene acetal yielded the diol which was used immediately after generation.

The 17β-stannylmethacrylate 3-iodoacetal template **12(β)** was reacted with both pyrrolidine acrylamide and 2(*R*),5(*R*)-dimethylpyrrolidine acrylamide by photolytic initiation with hexabutylditin. The products of reaction with pyrrolidine acrylamide were subjected to exhaustive analysis by fast atom bombardment mass spectrometry, with no evidence for the desired macrocycles. In fact, no series of ions differing by the mass of the monomer were observed at all. Chromatographic analysis by gel permeation chromatography (GPC) showed the vast body of the product to elute at a similar retention time to a 30 000 average molecular weight polystyrene standard. Proton NMR of the product showed broad diffuse signals characteristic of polymers at room temperature. An identical analysis of the product mixture from reaction with dimethylpyrrolidine acrylamide yielded identical results.

Reaction of the iodoacetal template **12(α)** was first performed with a commercially available, volatile monomer. Methyl methacrylate was chosen for its high reactivity and for its tendency to form atactic polymers. The reaction, as shown in Scheme IV, was performed by photolytic initiation of **12(α)** at 0.5 mM and methyl methacrylate at 10 mM. Lower concentrations were used because of the higher reactivity of methyl methacrylate relative to the acrylamides. After removal of the olefin at reduced pressure, the tin byproducts were removed by a crude silica gel separation (with all products then being combined). Mass spectral analysis by thermospray injection and methane/ammonia chemical ionization showed the ammonium adduct of the $n = 4$ macrocycle and trace amounts of the ion appropriate for the $n = 3$ macrocycle. The products were a chromatographically and spectroscopically very complex mixture, as expected, due to the numerous stereoisomers present. To further corroborate the formation of macrocycles, the product mixture was subjected to acidic hydrolysis. Refluxing in acidic methanol gave a product which showed mass spectral signals appropriate for the $n = 3$ and $n = 4$ lactonized oligomer **13**, in addition to androstanolone dimethyl acetal.

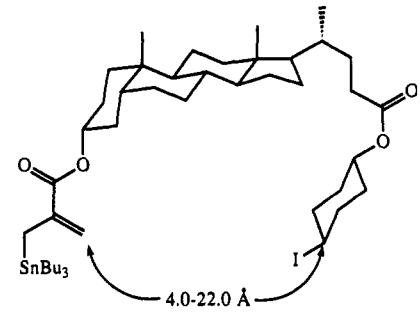
(18) Baggett, N.; Brimacombe, J. S.; Foster, A. B.; Stacey, M.; Whiffen, D. H. *J. Chem. Soc.* **1960**, 2574–2581.

Reaction of iodoacetal template 12($\alpha$) was also performed with chiral monomers. Reaction with 2(*R*),5(*R*)-dimethylpyrrolidine acrylamide 6 produced a glassy solid which proved insoluble in every solvent and solvent mixture tried. Reaction was also performed with an oxazolidine acrylamide, analogous to 7, but with a *tert*-butyl rather than a phenyl substituent. The product from this reaction was obtained as a fine white powder which was sparingly soluble in THF and chloroform. The GPC retention time for this product was again similar to that for 30 000 average molecular weight polystyrene standard. No part of the reaction mixture produced a GPC peak at a retention time appropriate for any macrocycle $n = 10$ or less.

## Discussion

**Kinetics.** Kinetic analysis of the reactions involved in the alkyl iodide/tin methacrylate templates shows them to be viable for macrocyclic oligomerization. After formation of the initial alkyl radical, the only relevant competition is between addition to monomer, intramolecular addition to tin methacrylate, and intermolecular addition to tin methacrylate. The rate of addition of all intermediate radicals will be slightly higher for reaction with tin methacrylate than acrylamide. Giese measured the rate of cyclohexyl radical addition to methyl methacrylate as 4.6 times the rate of addition to acrylamide,[19] and the copolymerization reactivity ratio for *N,N*-dimethylacrylamide polymer addition to methyl methacrylate is in the range of 0.41–0.59.[20] A higher monomer concentration can easily compensate for these relatively small kinetic differences. Successful macrocyclization relies on a high effective concentration of the tethered tin methacrylate relative to the propagating radical at some point during the oligomerization. Addition of a radical to the tin methacrylate is very rapidly followed by $\beta$-scission of the tributyltin radical. For successful chain reaction propagation, the tin radical must react preferentially with the iodide. The rate of addition of tributyltin radical to methyl methacrylate has been measured at $1.2 \times 10^8$ $M^{-1}$ $s^{-1}$ at 25 °C, and iodine abstraction from methyl iodide by tributyltin radical has been measured as $4.3 \times 10^9$ $M^{-1}$ $s^{-1}$ at 25 °C while abstraction from cyclohexyl iodide would be expected to be close to diffusion controlled.[21] In order to maximize chain lengths, very reactive iodides should be used whenever possible. For this reason, secondary iodides were used even when they brought about stereochemical complications in the products. We note that macrocycles have been produced using an $S_Hi$ process with allylstannanes.[14b]

**Iodocyclohexyl Template.** A prediction of the smallest oligomer that could span the initiator–terminator gap was made for each template by performing a computational conformational search. The SYBYL[22] search routine was used with creation of a one-dimensional distance map; that is, the initiator to terminator distance was determined for each conformation. The steroid was constrained to be in its lowest energy conformation, with rotation of only the side chains and substituents allowed. For simplicity, the tin methacrylate was modeled as an unsubstituted acrylate. The distance evaluated was from the carbon which would bear the free radical to the terminal carbon of the acrylate. Figure 5 shows iodocyclohexyl template 4 and the calculated distance range of 4.0–22.0 Å. As an approximation of the distance spanned by a particular size oligomer, the length of perfectly staggered hydrocarbon chains with the appropriate number of methylene units were calculated.




| *n* | distance Å |
|---|---|
| 1 | 3.9 |
| 2 | 6.3 |
| 3 | 8.8 |
| 4 | 11.3 |

**Figure 5.** *Iniator–terminator gap size for iodocyclohexyl template 4.*

Iodocyclohexyl template 4 can achieve an initiator–terminator distance of just 4.0 Å, and thus it has a good chance of forming the $n = 1$ macrocycle. It should be noted that the 0.1-Å discrepancy in this prediction is insignificant. These models are meant as very rough indicators of gap size and conformational lability. These calculations of gap size are flawed in several ways. First, they treat the steroid as perfectly rigid. There is certainly some flexibility in the steroid skeleton which could allow significant deviation from the measured distances. The distance is also measured as a shortest distance straight line, with no consideration of the conformational flexibility of an oligomer spanning the gap.

A more reasonable model might involve conformational searching of bound oligomers, looking for the minimum chain length producing a conformation which places the propagating radical within reacting distance of the terminator. This model is only somewhat better, but it is computationally a much larger problem.

Iodocyclohexyl template 4 did indeed produce the $n = 1$ macrocycle in moderate yield upon reaction with all three acrylamides. Reaction with achiral monomer 5 produced four isomeric products, whereas reaction with dimethylpyrrolidine acrylamide 6 produced only two isomers. Acrylamide addition to the cyclohexyl radical apparently occurs with no preference for cis or trans addition relative to the acyloxy substituent. The dimethylpyrrolidine amide is apparently controlling the configuration at the $\alpha$-amide position, as there is no indication of minor isomers. An intermolecular addition of a radical substituted with the same auxiliary to ethyl acrylate occurred in 85% de at 80 °C.[10a] This reaction performed at 25 °C should be highly stereoselective.

The reaction of iodocyclohexyl template 4 with phenyloxazolidine acrylamide 7 was not so readily analyzed because the resulting macrocycles were inseparable by normal-phase HPLC and insoluble in reverse-phase solvents. Proton NMR analysis indicated the presence of only two products in the ratio of 1.9:1 as determined by integration of resolved signals. X-ray crystallographic

(19) Giese, B.; Meister, J. *Chem. Ber.* 1977, *110*, 2588.
(20) *Polymer Handbook*, 3rd ed.; Brandrup, J., Immergut, E. H., Eds.; Wiley: New York, 1989.
(21) Ingold, K. U.; Lusztyk, J.; Scaiano, J. C. *J. Am. Chem. Soc.* 1984, *106*, 343.
(22) Tripos Associates, 1990.

analysis of the major enantiomer (Figure 4) showed that cyclization occurred over the α-face of the steroid to give a $C_{28}$···$C_{31}$ distance of 3.878 (8) Å, not significantly different from the predicted value of 3.9 Å (see Figure 5). Bond lengths in the steroid rings [1.500 (9)–1.568 (9) Å] are in accord with expectations.[23] Endocyclic torsion angles[24] in rings A, B, and C range in magnitude from 51.8 (5)° to 59.5 (5)°, and all three rings have chair conformations with that of ring A being slightly flattened around $C_3$ and $C_4$ to accommodate the macrocyclic ring. Analysis of ring D torsion angles indicates that it has a conformation approximating more closely to an envelope form with $C_{13}$ as the out-of-plane atom than to half-chair form with its $C_2$ symemtry axis passing through $C_{16}$ and the midpoint of the $C_{13}$–$C_{14}$ bond. The slightly elongated $C_{20}$–$C_{22}$ bond [1.560 (5) Å] in the pseudoequatorially oriented steroid side chain reflects the presence of some bond strain in this region. The cis-substituted cyclohexyl ring is in a chair conformation that is flattened significantly at the center ($C_{34}$) bearing the axial acyloxy substituent. There is no reason to believe that addition of the cyclohexyl radical became selective with monomer 7. A more reasonable explanation is that conformational restrictions associated with one of the cyclohexyl adduct epimers makes macrocyclization less favorable. At the α-amide center ($C_{29}$), the stereochemistry is as predicted.[11] Bond distances in the phenyloxazoline amide correspond well with the means derived recently in our laboratories[11,26] from X-ray studies on a number of oxazolidines.

**Iodopropyl and Iodoacetate Templates.** In order to encourage the formation of larger macrocycles, shorter iodide units were incorporated. Iodopropyl template **9** retained a secondary iodide for kinetic purposes, with the concomitant stereochemical complication, whereas iodoacetate template **10** produced no extra stereocenter at the risk of making it an inefficient macrocycle precursor. Templates **9** and **10** both have nearly identical minimum initiator–terminator gap sizes, 5.8 and 5.7 Å, respectively. From this gap, it is predicted that macrocycles would be formed with a minimum of two monomers incorporated. The detection of $n = 1$ macrocycle for all reactions of **9** and **10** is an indication of the degree of flexibility of the steroid skeleton, especially with the cis A–B ring fusion of the lithocholates. The cis A–B ring fusion allows any motion of the A ring toward a boat conformation to bring the initiator and terminator closer on the α-face. The same motion of a trans A–B fused steroid would actually increase the distance between substituents across the α-face.

Templates **9** and **10** both produced some $n = 1$ macrocycle, but the ion in the mass spectrum derived from the $n = 2$ macrocycle was the most abundant for both cyclizations with pyrrolidine acrylamide. Both reactions with achiral monomer produced significant amounts of $n = 3$ and $n = 4$ macrocycle. Since the HPLC/MS interface is expected to become less efficient at transporting higher molecular weight components of the product mixture, and since mass spectral response factors are not known for these compounds, quantitative evaluation of macrocycle size distribution cannot be made from HPLC/MS analysis. The mass chromatograms also show that the different size macrocycles are not being resolved by reverse-phase HPLC. Attempts to separate products by gel permeation chromatography also failed. Despite this failure, it is safe to say that iodopropyl template **9** and iodoacetate template **10** both produce a range of different size macrocycles with the distribution skewed significantly toward larger macrocycles when compared to the products derived from iodocyclohexyl template **4**.

The mass chromatograms of the macrocyclic products of iodopropyl template **9** reaction with pyrrolidine acrylamide show product mixtures of a complexity commensurate with the $2^{(n+1)}$ possible stereoisomers. Mass chromatograms of the products of the same reaction of iodoacetate template **10** show the predicted simplification for 2-fold reduction of possible macrocycle stereoisomers. Unfortunately, simplification of the product mixture was overshadowed by a large reduction in the yield of macrocycles. Apparently, the iodoacetate is not a fast enough iodine atom donor to produce an efficient free radical chain reaction.

Reaction of iodopropyl template **9** with dimethylpyrrolidine acrylamide produced $n = 1$, $n = 2$, and $n = 3$ macrocycles. The mass spectral abundances of the three products were similar by HPLC/MS, and the mass chromatograms for this reaction were significantly simplified relative to those for the reaction of **9** with achiral monomer. The mass chromatograms for $n = 1$ and $n = 2$ macrocycle appear as two major peaks with a smaller unresolved portion due to minor stereoisomers. There are still $2^{(n+1)}$ possible stereoisomers for each macrocycle; however, only one stereogenic center is being formed without stereocontrol.

The lithocholate templates demonstrated the feasibility of multiple olefin incorporating macrocyclizations by iodide/tin methacrylate spanning oligomerization templates and the potential for combining this strategy with stereoselective oligomerization techniques was also demonstrated. The lithocholate templates had some serious flaws as the secondary iodides used produced uncontrolled stereogenic centers. The initiator–terminator gaps produced by these templates were insufficient to prevent $n = 1$ macrocyclization, and when the templates were modified to produce larger macrocycles, a distribution of different sizes resulted. Lithocholic acid itself has the intrinsic disadvantages of a cis A–B ring fusion, adding flexibility and reducing gap sizes, and a long conformationally labile side chain, allowing a broad range of macrocycle sizes.

**Androstanolone Iodoacetal Templates.** The next templates targeted sought to correct all of these flaws. Iodoacetal templates **12**(α) and **12**(β) and their calculated initiator–terminator distances are shown in Figures 6 and 7, respectively. The secondary iodoacetal initiators do introduce an uncontrolled stereocenter. In theory, however, this stereocenter could be destroyed by hydrolysis of the acetal after macrocyclization. The all-trans steroid produces larger initiator–terminator gaps and should be

(23) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.

(24) Endocyclic torsion angles ($\omega_{ij}$, $\sigma \pm 0.4$–$0.8°$) about the bonds between atoms *i* and *j* in **8c** follow: $\omega_{1,2}$ 57.2, $\omega_{2,3}$ −53.8, $\omega_{3,4}$ 51.8, $\omega_{4,5}$ −52.1, $\omega_{5,10}$ 53.6, $\omega_{10,1}$ −57.2 in ring A; $\omega_{5,6}$ −56.3, $\omega_{6,7}$ 53.0, $\omega_{7,8}$ −52.1, $\omega_{8,9}$ 54.5, $\omega_{9,10}$ −56.3, $\omega_{10,5}$ 57.3 in ring B; $\omega_{8,9}$ −56.1, $\omega_{9,11}$ 56.6, $\omega_{11,12}$ −55.1, $\omega_{12,13}$ 53.0, $\omega_{13,14}$ −58.0, $\omega_{14,8}$ 59.5 in ring C; $\omega_{13,14}$ 49.0, $\omega_{14,15}$ −34.4, $\omega_{15,16}$ 6.3, $\omega_{16,17}$ 22.9, $\omega_{17,13}$ −43.0 in ring B; $\omega_{31,32}$ 54.0, $\omega_{32,33}$ −51.8, $\omega_{33,34}$ 45.9, $\omega_{34,35}$ −46.2, $\omega_{35,36}$ 52.5, $\omega_{36,31}$ −54.4 in the cyclohexyl moiety; $\omega_{38,54}$ −1.7, $\omega_{54,42}$ −20.2, $\omega_{42,41}$ 35.3, $\omega_{41,55}$ −39.7, $\omega_{55,38}$ 25.8 in the oxazoline ring.

(25) Bond lengths ($\sigma$ 0.005–0.007 Å) in **8c** with, in parentheses, corresponding means for eight oxazolidine moieties follow: $C_{38}$–$N_{54}$ 1.491 (1.492), $C_{38}$–$O_{55}$ 1.440 (1.425), $C_{41}$–$C_{42}$ 1.524 (1.528), $C_{41}$–$O_{55}$ 1.405 (1.417), $C_{42}$–$N_{54}$ 1.470 (1.473), $C_{37}$–$N_{54}$ 1.364 (1.352), $C_{37}$–$O_{53}$ 1.227 (1.225).

(26) Porter, N. A.; Rosenstein, I. J.; Breyer, R. A.; Bruhnke, J. D.; Wu, W.-X.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664.

(27) *International Tables for X-Ray Crystallography*; The Kynoch Press: Birmingham, England, 1974; Vol. IV.

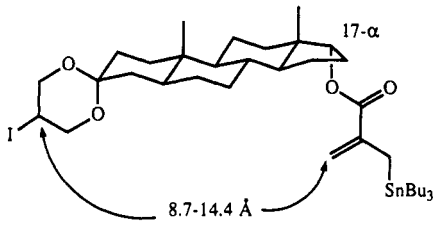



**Figure 6.** Initiator–terminator gap size for iodoacetal template 12(α).

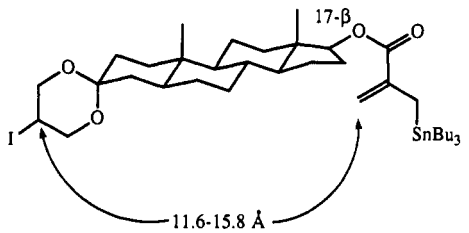



**Figure 7.** Initiator–terminator gap size for iodoacetal template 12(β).

more rigid. Minimum initiator–terminator gaps are similar to the distance spanned by 3 and 4 unit oligomers for 12(α) and 12(β), respectively. Initiator and terminator substituents produce minimal conformational lability as shown by the small range of gap sizes, and inversion of the 17-hydroxy substituent allows access to two different gap sizes via a trivial modification.

All reactions of 12(α) and 12(β) with chiral monomers produced large amounts of polymeric material. Exhaustive searching for macrocycles by fast atom bombardment mass spectrometry revealed no ions in the mass range appropriate for macrocycles size 1–10. Chromatographic analysis of the products by GPC showed no product with a retention time appropriate for macrocycles and much material with retention appropriate for polymer. The one successful reaction paired iodoacetal 12(α) with methyl methacrylate, generating $n = 3$ and $n = 4$ macrocycle. Analysis was hampered by the large number of stereoisomeric products formed and by instability of the acetal during reverse-phase HPLC separation. Destruction of the stereogenic center of the acetal was even impossible due to lactonization of the diol with the oligomer during hydrolysis from the steroid.

The moderate success attained by reaction of 12(α) with methyl methacrylate, and the complete failure with chiral olefins, suggests difficulty arising from the conformation and steric bulk of the oligomers formed. Conceptualizing the spanning oligomer as an unsubstituted hydrocarbon chain is a gross oversimplification. Crystal structures of telomers of these chiral monomers show the oligomer backbone in a helical conformation, with the chiral amides out, forming a large cylinder.[11] The necessary proximity of the oligomer and the steroid for successful macrocyclization of 12(α) and 12(β) would be discouraged by the bulky oligomer. Also, if the oligomer helix had some directionality, that is, a tendency to grow in one direction, an inflexible initiator, like the iodoacetal, might prevent the oligomer from approaching the terminator. Simply put, because of steric hindrance and conformational inflexibility, the effective relative concentration of the propagating radical and the tethered terminator might be zero. Successful macrocyclization in the reaction of 12(α) with methyl methacrylate can be explained by the combination of a less sterically bulky spanning oligomer and the ability of the atactic polymer to propagate, at least partially, in the direction of the terminator. As was noted earlier, Feldman's template produced only six of the eight possible stereoisomers in a 5:5:19:9:8:54 ratio.

## Conclusions

The conformational flexibility which was blamed for the polydispersity of the macrocycles obtained from the lithocholate templates may have been essential to their success. Subsequent template design should give special attention to providing the initiator group with some degree of directional mobility. It is also worth noting that because of the cis A–B ring fusion of the lithocholates, the terminator was a greater distance behind the α-face of the steroid than it would be for a similarly substituted all-trans steroid. This geometry might be critical in allowing a bulky oligomer to approach the terminator without excessive hindrance from the steroid.

Although the goals of a spanning oligomerization template may seem somewhat incompatible with the physical character of the oligomers of the chiral acrylamides, this work has, by two extreme examples, pointed out several pit-falls which were not fully recognized prior to these studies. The successful production of various sizes of monomer-incorporated macrocycles does demonstrate the feasibility of this strategy with alkyl iodide initiators and a tin methacrylate terminator.

## Experimental Section

**General Procedures.** Tetrahydrofuran was freshly distilled from sodium benzophenone. Dichloromethane was distilled from calcium hydride and stored over molecular sieves. Benzene was distilled from sodium and stored over molecular sieves. Gas chromatography was performed on a Hewlett-Packard 5890A gas chromatograph with a flame ionization detector coupled to a Hewlett-Packard 3393A integrator (conditions: 15-m 0.32-mm-i.d. SPB-1 column, 5 psi, 1 min at 100–280 °C at 15 °C/min). Analytical normal-phase HPLC was performed using a Waters M6000 pump, tandem Beckman Ultrasphere Si-4.6-mm × 25-cm columns, and a Waters R401 differential refractometer. Preparative normal-phase HPLC was performed using an Isco 2350 pump, a Dynamax 60A Si 83-121-C5 silica column, and a Waters R401 differential refractometer. Analytical reverse-phase HPLC was performed using a Waters M6000 pump, tandem Beckman ODS 4.6-mm × 25-cm columns, and a Waters R401 differential refractometer. Preparative reverse-phase HPLC was performed using a Waters M6000 pump, Dynamax C-18 column, and a Waters R401 differential refractometer. Gel permeation chromatography (GPC) was performed using a Waters 600E pump, tandem 100 and 500 Å 7.8- × 300-mm Ultrastyragel columns, and a Waters 441 UV detector at 254 nm, with tetrahydrofuran as eluting solvent. HPLC mass spectra were obtained on a Hewlett-Packard 5988A mass spectrometer and the analytical reverse-phase apparatus detailed above coupled via a Hewlett-Packard 59980A particle beam LC/MS interface. Unless otherwise specified, reagents were used as supplied from Aldrich Chemical Co.

The acrylamides **5**, **6**, and **7** were prepared as described previously[11] and α-(tributylstannyl)methacryloyl chloride was prepared essentially by the method of Baldwin.[14c]

**3α-(*tert*-Butyldimethylsiloxy)-5β-cholan-24-oic Acid (1).**[12] Lithocholic acid (8.62 g, 22.9 mmol) was dissolved in 80 mL of dry DMF. With stirring under argon, TBDMSCl (13.8 g, 91.6 mmol) was added at once followed by portionwise addition of imidazole (12.53 g, 184 mmol). The mixture was stirred at 40 °C for 4 h. After cooling to room temperature the reaction mixture was added to 1 L of saturated aqueous NaCl. The aqueous solution was washed three times with hexane. The combined organic extracts were washed with ice-cold 1 N HCl followed by saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure yielding 17.7 g of clear oil which

smelled strongly of TBDMSCl. This oil was used in the next step without purification.

The crude TBDMS ether/TBDMS ester was dissolved in 300 mL of methanol and 100 mL of THF. $K_2CO_3$ (10 g in 100 mL of water) was added with stirring. The mixture was stirred for 1 h, after which it was concentrated to one-quarter volume and diluted with 300 mL of saturated aqueous NaCl. The aqueous mixture was acidified to pH 4 with 1 N $KHSO_4$ and was extracted twice with dichloromethane. The combined organic washes were dried over $MgSO_4$, filtered, and concentrated under reduced pressure yielding 11.05 g of a white solid. Recrystallization from $CHCl_3$ provided 10.65 g of white solid (95% yield): mp 88–91 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.57 (m, 1 H), 2.45–2.15 (2), 1.97–0.95 (26), 0.92–0.85 (6), 0.868 (s, 9 H), 0.611 (s, 3 H), 0.036 (s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 180.55, 72.86, 56.35, 55.92, 42.70, 42.26, 40.13, 40.10, 36.84, 35.82, 35.56, 35.32, 34.56, 31.07, 30.96, 30.73, 28.17, 27.27, 26.37, 26.07, 26.00, 25.94, 24.19, 23.39, 23.34, 20.78, 18.34, 18.22, 12.05, 11.98, −4.62.

***trans*-4-Iodocyclohexanol.**[13] 7-Oxabicyclo[2.2.1]heptane was added dropwise to 25 mL of 47% HI at room temperature and was stirred for 1 h. The reaction mixture was diluted with 50 mL of water and was washed thoroughly with diethyl ether. The ethereal solutions were washed with aqueous $Na_2S_2O_3$ and then saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was eluted through silica in 20% EtOAc/hexane, yielding a yellow oil which solidified on standing to 3.20 g of a yellow waxy solid (69% yield): mp 54–55 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.18 (m, 1 H), 3.72 (m, 1 H), 2.26 (m, 2 H), 2.00–1.80 (4), 1.56 (s, 1 H), 1.39 (m, 2 H); $^{13}$C NMR (75 Hz, $CDCl_3$) $\delta$ 68.06, 36.66, 36.36, 35.86; MS (GC/CI) *m/e* 244 (42), 226 (33), 209 (85), 116 (78), 99 (75), 98 (100).

**3α-(*tert*-Butyldimethylsiloxy)-5β-cholan-24-oic Acid *trans*-4-Iodocyclohexyl Ester (2).** Protected lithocholic acid 1 (2.94 g, 6.0 mmol) was combined with iodocyclohexanol (1.6 g, 7.1 mmol) and 0.71 mmol of DMAP (75 mg) in 125 mL of dry diethyl ether. Dicyclohexylcarbodiimide (1.46 g, 7.1 mmol) was added, and the mixture was stirred for 12 h at room temperature under argon. The reaction mixture was then filtered, concentrated under reduced pressure, and purified by elution through silica with 2% EtOAc/hexane yielding 1.60 g of white solid (38% yield): $R_f$ 0.63 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.77 (m, 1 H), 4.27 (m, 1 H), 3.52 (m, 1 H), 2.35–0.90 (36), 0.90–0.80 (6), 0.84 (s, 9 H), 0.57 (s, 3 H), 0.00 (s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.44, 72.76, 69.80, 56.36, 55.90, 42.68, 42.23, 40.15, 36.87, 35.81, 35.56, 35.28, 34.54, 31.50, 31.41, 31.00, 28.20, 27.27, 26.39, 26.01, 25.97, 24.20, 23.42, 23.39, 20.79, 18.31, 18.26, 12.04, 12.02, −4.56. Anal. Calcd for $C_{36}H_{63}IO_3Si$: C, 61.87; H, 9.09; I, 18.16. Found: C, 61.75; H, 9.05; I, 18.28.

**3α-Hydroxy-5β-cholan-24-oic Acid *trans*-4-Iodocyclohexyl Ester (3).** The silyl ether 2 (1.6 g, 2.3 mmol) was dissolved in a minimum amount of acetonitrile (~200 mL) with gentle warming. A 10-mL portion of 50% HF was added dropwise, and the mixture was warmed until it was once again homogeneous. Water was added until a solid precipitate began to form, and the mixture was cooled to 0 °C. After several minutes, the solid was removed by vacuum filtration and washed with water. The solid was dissolved in dichloromethane, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by elution through silica with 25% EtOAc/hexane yielding 1.30 g of white solid that softened at temperatures above 45 °C (97% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.80 (m, 1 H), 4.30 (m, 1 H), 3.61 (m, 1 H), 2.35–0.93 (36), 0.89 (s, 3 H), 0.88 (d, $J$ = 6.6 Hz, 3 H), 0.61 (s, 3 H); MS (DIP/CI) *m/e* 602 (59), 584 (11), 567 (12), 476 (100), 376 (27), 359 (37). Anal. Calcd for $C_{30}H_{49}IO_3$: C, 61.63; H, 8.45; I, 21.71. Found: C, 61.68; H, 8.45; I, 21.79.

**3α-Hydroxy-5β-cholan-24-oic Acid 3-(α-(Tributylstannyl)methacrylate) 24-(*trans*-4-Iodocyclohexyl ester) (4).** The sterol 3 (0.20 g, 0.34 mmol) was combined with 0.25 mL of pyridine in 6 mL of dry, degassed benzene. The acid chloride was added in 3 mL of benzene, and the mixture was stirred under argon in the dark for 12 h. The reaction mixture was then filtered through silica in 5% EtOAc/hexane. After concentrating under reduced pressure, the residue was eluted through silica in 2% EtOAc/hexane, with further purification performed by preparative HPLC in 2% EtOAc/hexane. This procedure yielded 187 mg of a clear oil (58% yield): Prep. HPLC $t_R$ 18 min (2% EtOAc/hexane, 12 mL/min), $R_f$ 0.52 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.77 (s, 1 H), 5.24 (s, 1 H), 4.81 (m, 1 H), 4.75 (m, 1 H), 4.30 (m, 1 H), 1.94 (s, 2 H), 2.35–0.95 (48), 0.95–0.75 (21), 0.618 (s, 3 H); IR ($CHCl_3$) 3020, 2938, 1711, 1216 cm$^{-1}$. Anal. Calcd for $C_{46}H_{79}O_4ISn$: C, 58.67; H, 8.46. Found: C, 58.83; H, 8.54.

**Iodopropyl Ester 9. 2-Bromo-1-propanol.**[16] Lithium aluminum hydride (3.42 g, 0.09 mol) was suspended in 125 mL of dry diethyl ether. Bromopropionyl bromide (2.06 g, 0.15 mol) was added dropwise at 0 °C with stirring under Ar over 20 min. The reaction mixture was allowed to warm up to room temperature and was stirred another 15 min, after which several milliliters of water were added as rapidly as possible without violent eruption. An excess of 10% $H_2SO_4$ was then added rapidly. The organic phase was separated, and the aqueous was washed twice with diethyl ether. The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was distilled yielding 16.77 g of a clear oil (80% yield): bp 58–60 °C (20 mmHg) (lit. bp 62.8–64.0 °C (24 mm)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.22 (m, 1 H), 3.74 (dd, $J$ = 12.0, 3.9 Hz, 1 H), 3.66 (dd, $J$ = 12.0, 6.9 Hz, 1 H), 2.04 (s, 1 H), 1.67 (d, $J$ = 6.9 Hz, 3 H).

**2-Iodo-1-propanol.** The bromide from above (16.7 g, 0.12 mol) and 1 equiv of NaI (18 g, 0.12 mol) were combined in 80 mL of acetone and were refluxed under Ar for 48 h. The mixture was then cooled and concentrated under reduced pressure. The residue was combined with dichloromethane and filtered. The solids were washed with dichloromethane. The combined dichloromethane solutions were washed with 1 N aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, backwashing each once with dichloromethane. The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was distilled, producing a dark red oil. This product was redissolved in dichloromethane and worked up as before yielding 16.4 g of a clear oil (74% yield): bp 58–60 °C (20 mmHg) (lit. bp 74–79 °C (20 mm)); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.22 (m, 1 H), 3.74 (dd, $J$ = 12.0, 3.9 Hz, 1 H), 3.66 (dd, $J$ = 12.0, 6.9 Hz, 1 H), 2.04 (s, 1 H), 1.67 (d, $J$ = 6.9 Hz, 3 H).

**3α-(*tert*-Butyldimethylsiloxy)-5β-cholan-24-oic Acid 2-Iodopropyl Ester.** The protected lithocholic acid 1 (2.45 g, 5.0 mmol) was combined with 2-iodopropanol (1.12 g, 6.0 mmol) and 0.2 equiv of DMAP (122 mg) in 40 mL of dry THF. Dicyclohexylcarbodiimide (1.24 g, 6.0mmol) was added in 10 mL of THF, and the mixture was stirred for 12 h at room temperature under argon. The reaction mixture was then filtered, concentrated under reduced pressure, and purified by elution through silica in 2% EtOAc/hexane yielding 0.56 g of white solid (17% yield): mp 74–77 °C; $R_f$ 0.66 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.24 (m, 1 H), 4.08 (m, 1 H), 3.52 (m, 1 H), 3.14 (m, 1 H), 2.44–2.10 (2), 1.94–0.92 (26), 1.86 (d, $J$ = 6.6 Hz, 3 H), 0.92–0.76 (15), 0.60 (s, 3 H), 0.02 (s, 6 H).

**3α-Hydroxy-5β-cholan-24-oic Acid 2-Iodopropyl Ester.** The silyl ether from above (0.56 g, 0.83 mmol) was dissolved in 2 mL of THF and 20 mL of $CH_3CN$. Two milliliters of 50% HF were added dropwise. The mixture was stirred for 1 h and was then added to 150 mL of saturated aqueous NaCl. The aqueous mixture was washed twice with dichloromethane which was in turn washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by elution through silica in 20% EtOAc/hexane yielding 0.276 g of yellow glassy solid (59% yield): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.25 (m, 1 H), 4.21 (m, 1 H), 4.10 (m, 1 H), 3.58 (m, 1 H), 2.36 (m, 1 H), 2.22 (m, 1 H), 1.95–0.92 (26), 1.85 (d, $J$ = 6.3 Hz, 3 H), 0.89 (d, $J$ = 5.1 Hz, 3 H), 0.88 (s, 3 H), 0.604 (s, 3 H); MS (DIP/CI) *m/e* 562 (86), 436 (88), 408 (100). Anal. Calcd for $C_{27}H_{45}IO_3$: C, 59.55; H, 8.33; I, 23.30. Found: C, 59.40; H, 8.38; I, 23.44.

**3α-Hydroxy-5β-cholan-24-oic Acid 3-(α-(Tributylstannyl)methacrylate) 24-(2-Iodopropyl ester) (9).** The sterol from above (0.202 g, 0.37 mmol) was combined with 0.30 mL of pyridine in 10 mL of dry, degassed benzene. The acid chloride was added in 3 mL of benzene, and the mixture was stirred under argon in the dark for 12 h. The reaction mixture was then diluted with 25 mL of hexane and was washed with 1 N HCl and saturated aqueous NaCl. The organic solution was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was eluted through silica in 2% EtOAc/hexane, with

further purification performed by preparative HPLC in 2% EtOAc/hexane. This yielded 191 mg of a clear oil (57% yield): Prep. HPLC $t_R$ 22 min (2% EtOAc/hexane, 10 mL/min); $R_f$ 0.52 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 6.10 (s, 1 H), 5.20 (s, 1 H), 4.96 (m, 1 H), 4.04 (m, 1 H), 3.92 (m, 1 H), 3.84 (m, 1 H), 2.16 (s, 2 H), 2.36–0.90 (55), 0.85 (d, 3 H), 0.78 (s, 3 H), 0.54 (s, 3 H). Anal. Calcd for $C_{43}H_{75}O_4ISn$: C, 57.28; H, 8.38. Found: 57.25; H, 8.40.

**Iodoacetate Template 10. 3α-(*tert*-Butyldimethylsiloxy)-5β-cholan-24-ol.**[17] The silyl-protected lithocholic acid 1 (2.0 g, 4.075 mmol) was dissolved in 25 mL of dry THF. Borane (6.11 mL, 1.0 M in THF) was added with stirring at 0 °C under argon. The solution was stirred at room temperature for 5 h, after which 25 mL of water was added dropwise. This mixture was saturated with $K_2CO_3$, and the organic layer was separated. The aqueous layer was washed three times with diethyl ether, and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The crude product was purified by elution through silica in 10% EtOAc/hexane yielding 1.82 g of a white foam that softened at temperatures above 60 °C (94% yield): $R_f$ 0.23 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.59 (m, 2 H), 3.54 (m, 1 H), 1.96–0.92 (28), 0.90 (d, $J$ = 5.8 Hz, 3 H), 0.872 (s, 3 H), 0.867 (s, 9 H), 0.61 (s, 3 H), 0.03 (s, 6 H); MS (LC/CI) *m/e* 495 (27), 477 (100), 345 (79), 327 (44).

**3α-(*tert*-Butyldimethylsiloxy)-5β-cholan-24-yl Iodoacetate.** The monoprotected diol from above (1.40 g, 2.94 mmol) was combined with 1 equiv each of DCC (0.607 g) and iodoacetic acid (0.547 g) and 36 mg (0.3 mmol) of DMAP in 20 mL of dry diethyl ether. The mixture was stirred at room temperature under argon for 12 h, after which it was filtered and concentrated under reduced pressure. The residue was purified by elution through silica in 5% EtOAc/hexane yielding 1.77 g of a clear oil (93% yield): $R_f$ 0.49 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.12 (m, 2 H), 3.68 (s, 2 H), 3.57 (m, 1 H), 1.96–0.92 (28), 0.92 (d, $J$ = 5.8 Hz, 3 H), 0.899 (s, 3 H), 0.896 (s, 9 H), 0.63 (s, 3 H), 0.07 (s, 6 H).

**5β-Cholane-3α,24-diol 24-Iodoacetate.** The iodoacetate from above (0.78 g, 1.21 mmol) was dissolved in 2 mL of THF and was diluted with 20 mL of $CH_3CN$. Two milliliters of 50% HF were added dropwise to the stirred solution. Stirring was continued until TLC showed complete disappearance of starting material (~1 h). The reaction mixture was then added to 150 mL of saturated aqueous NaCl which was, in turn, washed twice with dichloromethane. The organic solutions were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by elution through silica in 20% EtOAc/hexane yielding 0.556 g of a white foam (87% yield): $R_f$ 0.13 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.18 (m, 2 H), 3.66 (s, 2 H), 3.59 (m, 1 H), 0.95–0.92 (28), 0.89 (d, $J$ = 8.0 Hz, 3 H), 0.89 (s, 3 H), 0.62 (s, 3 H); MS (DIP/CI) *m/e* 548 (56), 422 (100). Anal. Calcd for $C_{26}H_{43}IO_3$: C, 58.86; H, 8.17; I, 23.92. Found: C, 58.75; H, 8.13; I, 24.02.

**5β-Cholan-3α,24-diol 3-(α-(Tributylstannyl)methacrylate) 24-Iodoacetate (10).** The sterol from above (0.524 g, 0.99 mmol) was combined with 0.80 mL of dry pyridine in 20 mL of dry, degassed benzene. Methacryloyl chloride (~1.5 mmol, from 0.56 g of ethyl ester) was added dropwise in 7.5 mL of benzene. The reaction mixture was stirred at room temperature under Ar for 5 h. The mixture was then diluted with 50 mL of hexane and was washed once each with 1 N HCl and saturated aqueous NaCl. The organic solution was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by elution through silica in 2% EtOAc/hexane followed by preparative HPLC in 2% EtOAc/hexane yielding 343 mg of a clear oil (39% yield): Prep. HPLC $t_R$ 22 min (2% EtOAc/hexane, 10 mL/min); $R_f$ 0.58 (20% EtOAc/hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.08 (s, 1 H), 5.27 (s, 1 H), 4.94 (m, 1 H), 3.91 (m, 2 H), 3.47 (s, 2 H), 2.14 (s, 2 H), 2.03–0.88 (28), 1.60 (m, 6 H), 1.38 (m, 6 H), 1.00 (m, 6 H), 0.94 (t, $J$ = 7.2 Hz, 9 H), 0.85 (d, $J$ = 6.3 Hz, 3 H), 0.79 (s, 3 H), 0.55 (s, 3 H). Anal. Calcd for $C_{43}H_{75}IO_4Sn$: C, 57.28; H, 8.38. Found: C, 57.25; H, 8.40.

**Reaction of Templates with Acrylamides 5, 6, or 7.** Systematic variation of the concentrations of template (0.1–50 mM) and olefin (10–100 mM) produced a maximum yield at 1 mM in template and 25 mM in olefin. Two methods of initiation were used and are illustrated here for the reaction of 4 with acrylamide 5.

Method 1 (ditin initiation): Template 4 (43 mg, 46 μmol) was combined with 139 μL (1.15 mmol) of 5 and 2.7 mg (4.6 μmol) of hexabutylditin in 46 mL of dry degassed benzene. The solution was stirred under Ar in a water-jacketed flask and was irradiated with a 250-W sun lamp until TLC showed complete disappearance of starting material (~3 h). The reaction solution was concentrated under reduced pressure, and the residue was filtered through silica in EtOAc. Polymeric material was washed off the silica in 1:1 $CH_2Cl_2$–MeOH. The EtOAc washings were concentrated, and the macrocycle was separated from olefin by preparative HPLC in EtOAc, yielding 15.2 mg of clear oil (51% yield).

Method 2 (borane initiation): Identical amounts of template 4 and olefin were combined in 46 mL of benzene. Triethylborane (5 μL, 1.0 M in hexane) was added, and the solution was stirred under air for 4 h. Purification was performed as above, also yielding 15.2 mg of product.

Due to the complexity of the product mixture, only characteristic NMR signals are listed, without integration: $R_f$ 0.30 (EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.18 (s), 6.12 (s), 6.11 (s), 5.60 (s), 5.47 (s), 5.23 (m), 5.19 (m), 4.92 (m), 4.72 (m), 4.61 (m), 3.40 (m), 3.22 (m), 0.97 (d, $J$ = 7.1 Hz), 0.91 (s), 0.90 (s), 0.89 (s), 0.98 (s), 0.84 (d, $J$ = 7.0 Hz), 0.65 (s), 0.63 (s); MS (DIP/CI) *m/e* 651 (M + H$^+$).

The reaction and workup of other templates and acrylamides was essentially the same as described above but for the template 4 and the acrylamide 7 the workup was modified as follows. The reaction solution was concentrated under reduced pressure, and the residue was eluted through silica in 20% EtOAc/hexane. Fractions containing macrocycle ($R_f$ 0.22 in 25% EtOAc/hexane) were heavily contaminated with olefin ($R_f$ 0.15 in 25% EtOAc/hexane). Most of the olefin was removed by crystallization from EtOAc/hexane (leaving the macrocycle in the mother liquor) and final purification was performed by preparative HPLC in 25% EtOAc/hexane yielding 47 mg of a white solid (31% yield). Repeated crystallization from $CH_2Cl_2$/MeOH produced a sample of the major stereoisomer suitable for X-ray analysis, see Figure 4. MS (DIP/CI) *m/e* 757 (M + H$^+$); accurate mass measurement in EI mode, calcd 755.5123, required for $C_{48}H_{69}NO_6$, 755.5125 (–0.3 ppm); prep. HPLC $t_R$ 19 min (25% EtOAc/hexane 10 mL/min). A ratio for the two major isomers was determined by $^1$H NMR, by comparing the integration of the vinylic signals at 5.56 and 5.51 ppm. This ratio was 1.0:1.9. The spectrum of the major isomer follows: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.35–7.15 (5 H), 6.23 (s, 1 H), 5.51 (s, 1 H), 5.02 (m, 1 H), 4.92 (m, 1 H), 4.70 (d, $J$ = 6.0 Hz, 1 H), 4.12 (dd, $J$ = 8.7, 6.0 Hz, 1 H), 3.70 (d, $J$ = 8.7 Hz, 1 H), 2.63–2.45 (3 H), 2.20–0.45 (39 H), 1.88 (s, 3 H), 1.57 (s, 3 H), 0.90 (d, $J$ = 6.3 Hz, 3 H), 0.89 (s, 3 H), 0.59 (s, 3 H).

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**Supplementary Material Available:** Synthetic procedures for 12α and 12β (9 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.