Table I. Bromination of 1 and 2 with "Onium" Tribromide at 0 °C[4]

ent	n	X	solvent	reaction time[8] (min)	3/4[a] or 5/6[b] ratio
1	1	tetrabutylammonium	CH_2Cl_2	10	56/44
2	1	tetraethylammonium	CH_2Cl_2	30	62/38
3	1	pyridinium	CH_2Cl_2	30	58/42
4	1	2,6-dimethylpyridinium	CH_2Cl_2	1	53/47
5	1	tetrabutylphosphonium	CH_2Cl_2	100	55/45
6	1	tetrabutylammonium	CH_3CN	5	85/15
7	1	tetraethylammonium	CH_3CN	30	86/14
8	1	tetrabutylphosphonium	CH_3CN	45	86/14
9	1	tetrabutylammonium	THF	60	94/6
10	1	tetraethylammonium	THF	30	95/5
11	1	pyridinium	THF	30	95/5
12	1	2,6-dimethylpyridinium	THF	30	95/5
13	1	tetrabutylphosphonium	THF	120	94/6
14	0	tetrabutylammonium	CH_3CN	1	80/20

[a] 3/4 ratio (3 + 4 = 95% yield) determined by ^{1}H-NMR (300 MHz, $CDCl_3$) at complete conversion of 1. The ratio does not change after several reaction times. [b] 5/6 ratio (5 + 6 = 81% yield) determined by ^{1}H-NMR (300 MHz, $CDCl_3$) at complete conversion of 2. The ratio becomes the equilibrium ratio 70/30.

epimer 3 having *R* configuration at the carbon bearing the bromine, strongly depends on the nature of the solvent, increasing in the following order: methylene chloride (de = 6), acetonitrile (de = 70), tetrahydrofuran (de = 88).

Other "onium" salts such as tetraethylammonium, pyridinium, 2,6-dimethylpyridinium, and tetra-*n*-butylphosphonium tribromides behave similarly in the bromination of 1 (see Table I). Thus, the diastereoselection is independent of the nature of the "onium" counterion.

Ketal 2 (n = 0) reacts at 0 °C in acetonitrile with tetra-*n*-butylammonium tribromide (Table I, entry 14) providing in 81% yield an epimeric mixture of α-bromo ketals 5 and 6. Epimer 5 of *R* configuration prevails over the other with a de (60) which approaches the one observed in acetonitrile for ketal 1 (Table I, entry 6).

Epimer 4 as well as 3, 4 mixtures of *any* epimeric composition kept under the above reaction conditions for several reaction times, were recovered quantitatively unchanged. The 5/6 ratio under the reaction conditions becomes the equilibrium ratio of 70/30.

From the above findings it comes out that the tribromide salt bromination of both 1 and 2 occurs under kinetically controlled conditions.

The sense of the diastereoselection with Br_3^- is opposite to that of the previously reported bromination of ketals 1 and 2 with bromine in methylene chloride (Table II, entry 1).[3d]

Table II. Bromination of 1 with Bromine[4]

ent	n	solvent	T (°C)	reaction time[8]	3/4 ratio
1	1	CH_2Cl_2	−10	10 s	12/88[a]
				1 h	25/75
				20 h	46/54[b]
2	1	CH_3CN	−10	30 min	22/78[a]
3	1	CH_3CN	15	1 min	29/71[a]
				3 min	30/70
				20 h	55/45[b]
4	1	THF	−10	30 min	1/99[c]
				40 min	42/58[b]

[a] 3/4 ratio determined by ^{1}H-NMR (300 MHz, $CDCl_3$) at complete conversion of 1. [b] Thermodynamic ratio. [c] 3/4 ratio determined at 20% conversion of 1.

For a more complete comparison between bromine and tribromide salts, the bromination of 1 with bromine was carried out in acetonitrile and in tetrahydrofuran (Table II, entries 2–4).

From the analysis of data reported in Table II (entries 2–4) it comes out that the bromination occurs under kinetically controlled conditions and that the sense of diastereoselectivity is independent of the nature of the solvent, the highest diastereoselectivity being observed in THF.

On the basis of the above findings it is possible to synthesize in high yield either one epimer or the other from the same ketal. This opens the route to the asymmetric synthesis of structurally related 2-bromo ketones[6] and 2-arylalkanoic acids[7] of both configurations in enantiomerically pure form by using the same chiral auxiliary [(2*R*,3*R*) tartaric acid].

The bromination of 1 and 2 underlines the difference between bromine and tribromide ion in electrophilic attack to activated alkenes.

The opposite diastereoselection observed between Br_2 and Br_3^- can be accounted for by the different electrophilicity of the two species and for the major ability of Br_2 vs Br_3^- to form charge-transfer complexes.

Work is in progress to extend the scope of the reaction and to clarify the reaction mechanisms.

Supplementary Material Available: Experimental procedures (1 page). Ordering information is given on any current masthead page.

(4) **General Experimental Procedure.** The brominating reagent (5 mmol) was added in one portion with stirring under nitrogen at the temperature given in the tables to a solution of 1 or 2 (5 mmol) in the solvent (10 mL). The reaction mixture was stirred for the time given in the tables. After workup with aqueous sodium carbonate mixtures of 3 and 4 or 5 and 6, in yields and in ratios given in the tables, were obtained.

(5) 2,6-Dimethylpyridinium tribromide, the only unknown compound (mp = 100–101 °C from acetic acid), has been prepared according to: Fieser, L. F.; Fieser M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 967.

(6) Castaldi, G.; Giordano, C. *Synthesis* **1987**, 1039.

(7) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *J. Org. Chem.* **1987**, *52*, 3018; *J. Org. Chem.* **1987**, *52*, 5642.

(8) It is likely that the rate-determining step of the reaction is the acid-catalyzed formation of the enol ether (Scheme I). In the absence of an acidic catalyst, an induction period is required until a trace of HBr is formed, which grows as soon as the bromination initiates. The nature of the solvent affects the acidity of the reaction medium and consequently the reaction time.

Synthesis of Macrocyclic Propargylic Alcohols by Ene-Type Cyclization of Unsaturated Acetylenic Aldehydes

James A. Marshall* and Marc W. Andersen

Department of Chemistry and Biochemistry, The University of South Carolina, Columbia, South Carolina 29208

Received March 2, 1992

Summary: Ene type cyclizations of ynals 6, 21, and 30 can be effected by $EtAlCl_2$ in CH_2Cl_2 at −78 °C to afford 14- and 12-membered homoallylic propargylic alcohols in 66–89% yield.

The continuing discovery of biologically important macrocyclic natural products has stimulated interest in developing cyclization methodology for rings of 12 or more members.[1] Several years ago, we reported that the in-

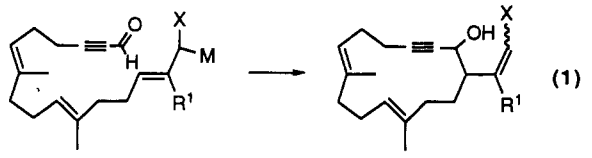
0022-3263/92/1957-2766$03.00/0

Table I. Cyclization of Ynal 6

Lewis acid	equiv	M	condns[a]	time, h	yield, %	7:8
$EtAlCl_2$	1.5	0.01	A	0.2	35	1:1
	1.0	0.01	A	0.2	64–75[b]	1:1
	1.0	0.001	A	0.5	67	1:1
	1.0	0.005	B	0.5	75–80[b]	1:1
Me_2AlCl	1.0	0.005	B	2	c	1:1
	1.5	0.005	B	0.5	35–55[b]	1:1
$BF_3{\cdot}OEt_2$	2.0	0.005	B	12	40–50[b]	5:1

[a] A = Lewis acid added to aldehyde in CH_2Cl_2 at −78 °C. B = aldehyde added to Lewis acid in CH_2Cl_2 at −78 °C. [b] Range of several runs. [c] Incomplete reaction.

tramolecular S_E' addition of allylic stannanes to conjugated ynals, as illustrated by **I** → **III**, proceeds with high efficiency.[2] The success of this cyclization can, at least in



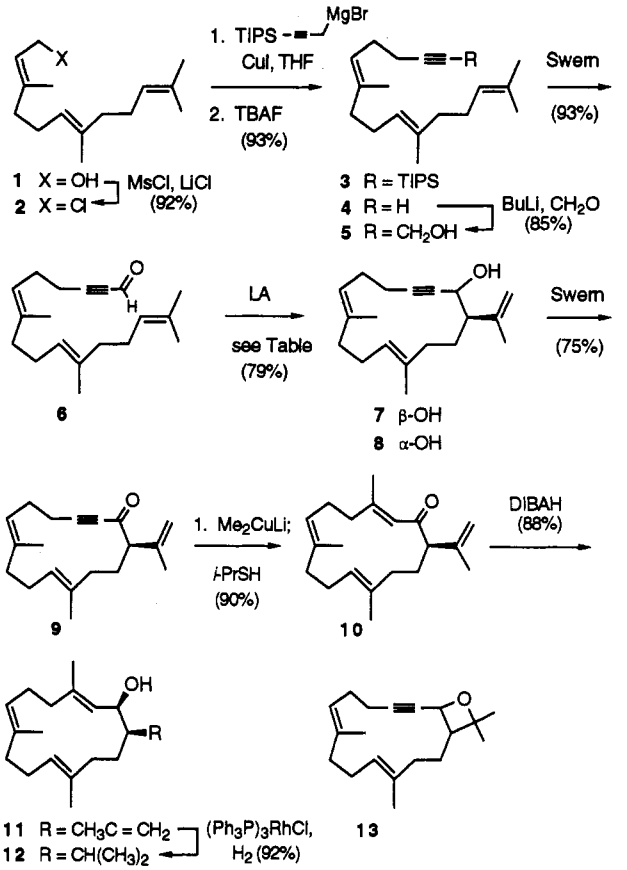
(1)

I ; R^1 = H, X = OMOM, M = $SnBu_3$ **III** R^1 = H, X = OMOM
II ; R^1 = Me, X = M = H **IV** R^1 = Me, X = H

part, be attributed to the high electrophilic reactivity of the ynal–Lewis acid complex and the entropic restrictions imposed by the alkyne and (*E*)-alkene linkages. In considering alternative strategies we were attracted to the possibility of the ene-type cyclization **II** → **IV**. The plan was appealing because of its directness and the ready availability of appropriate starting materials. However, such cyclizations had previously been successful only for five-, six-,[3] and a few conformationally constrained seven-membered rings,[4] and we were concerned that cyclization rates for larger rings might be too slow to compete with intermolecular additions and Lewis acid promoted product decomposition.[5]

For our feasibility study we selected farnesol (**1**) as the starting material. Cu(I)-catalyzed coupling of the chloride **2** with TIPS propargylmagnesium bromide, as previously described,[2] afforded the trienyne **3** as the only product in over 90% yield. Desilylation and then hydroformylation led to propargylic alcohol **5** which was smoothly oxidized to aldehyde **6** by the method of Swern.[6]

Cyclization of aldehyde **6** was examined with a number of Lewis acids under varying conditions as summarized in Table I. Best results were obtained by slow addition of the aldehyde to a dilute solution of Lewis acid in CH_2Cl_2 at −78 °C. Both $EtAlCl_2$ and Me_2AlCl[7] afforded 1:1 mixtures of cis and trans isomers **7** and **8**. With $BF_3{\cdot}OEt_2$, a 5:1 mixture was obtained but the yield was lower. The use of $SnCl_4$ or $TiCl_4$ led to extensive decomposition.[8] With



$ZnCl_2$ or $(i\text{-PrO})_2TiCl_2$ no reaction occurred, even at room temperature.

Cyclization with $EtAlCl_2$ was most efficient affording alcohols **7** and **8** in 75–80% yield. A third product, oxetane **13**, was also formed in this reaction in ca. 10% yield, thus accounting for nearly all of the starting aldehyde.[9] Conversion of propargylic alcohols **7** and **8** to racemic mukulol (**12**) was readily effected by well-precedented methodology.[2,10] Addition of the Gilman methyl cuprate to ynone **9** yielded a 90:10 mixture of *Z* and *E* enones when the reaction was quenched with methanol at −20 °C. A 1:1 mixture of *E* and *Z* enones resulted upon quenching with aqueous NH_4Cl. Quenching with *i*-PrSH at 0 °C to room temperature effected enone equilibration, and a 96:4 mixture favoring the *E* isomer **10** was thus produced. Reduction of enone **10** afforded the cis alcohol **11**. Of several hydrides surveyed DIBAH gave the most favorable cis–trans ratio of alcohol products (90:10). Homogeneous hydrogenation of this isopropenyl substituent completed the synthesis.

We next examined several applications of the foregoing cyclization methodology aimed at 12-membered propargylic alcohols. The first of these employed the isopropylidene ynal **21**, obtainable through a straightforward sequence from 4-pentynal (**14**). Cyclization with $EtAlCl_2$ at −78 °C, as for ynal **6**, led to an apparent 1.5:1 mixture of diastereomeric alcohols **22**, according to ^1H NMR and GC analysis, in 66% yield. Oxidation of alcohols **22** afforded a 1.5:1 mixture of ketones **24**. Reduction of this mixture with DIBAH yielded a mixture of cis and trans

(1) For a review of the major macrocyclization methods as applied to 14-membered cembranoid intermediates see: Tius, M. A. *Chem. Rev.* **1988**, *88*, 719.

(2) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616.

(3) *Cf.* Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2203. Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538.

(4) *Cf.* Marshall, J. A.; Andersen, N. H.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 186; Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858.

(5) For a recent review, see Snider, B. B. in **Comprehensive Organic Synthesis**. B. Trost, Ed., *Vol. 2*, Pergamon Press, N.Y., pp. 527–561.

(6) Omurka, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

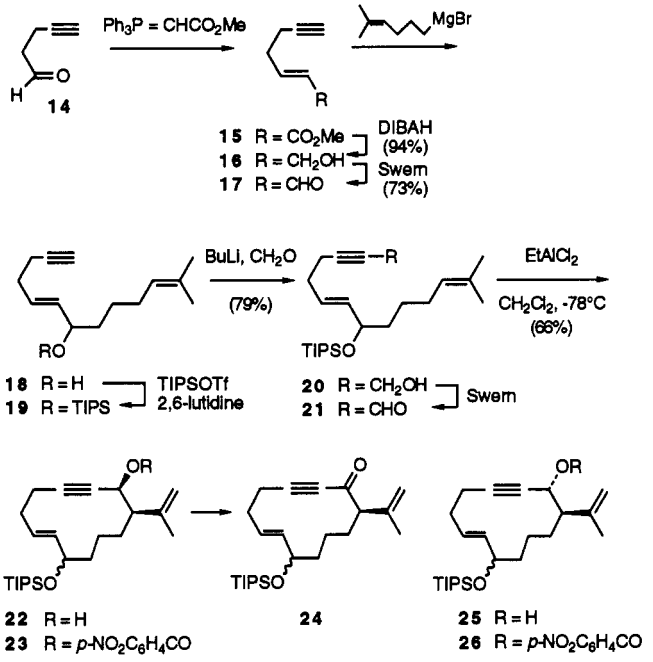
(7) For a discussion of the merits of these Lewis acids for ene reactions, see Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426–432.

(8) A related cyclization of geranylgeranoic acid chlorides to the 14-membered chloro ketones with $SnCl_4$ was described by Kato, *et al.* Kato, T.; Suzuki, M.; Kobayashi, T. *J. Org. Chem.* **1980**, *45*, 1126.

(9) For an additional example of oxetane formation under these conditions see Demole, E.; Enggist, P.; Borer, M. C. *Helv. Chim. Acta.* **1971**, *54*, 1845.

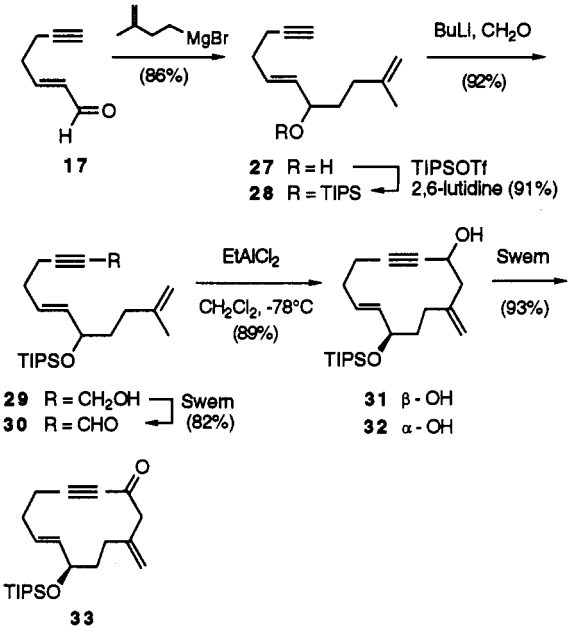
(10) Marshall, J. A.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 5081. Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1987**, *52*, 3860.

alcohols **22** and **25**. Careful chromatography of the alcohol mixture yielded a pure cis fraction, a mixed cis fraction, and a mixed trans fraction, **25**. The derived *p*-nitrobenzoates **23** and **26** showed coupling for the carbinyl



protons of ca. 4 (cis), 10.1 (major trans), and 8.9 Hz (minor trans). Coupling constants derived from molecular mechanics minimized structures were significantly lower for the diastereomeric cis isomers **22** vs trans isomers **25**.[11] In the absence of chemical correlations, these stereochemical assignments must be regarded as tentative. Interestingly, none of the trans isomers **25** could be detected in the ^1H NMR spectrum of the cyclization product **22**.

The isopropenyl ynal **30** underwent a facile type-II cyclization upon treatment with $EtAlCl_2$ in CH_2Cl_2 at −78 °C affording a 1:1 mixture of diastereomeric alcohols **31** and **32** in 89% yield. Upon oxidation this mixture afforded a single ketone **33** in 93% yield.



The foregoing preliminary results show that ene-type cyclizations can be employed for large as well as normal-size rings. Though less stereoselective than the related allylstannane methodology, the approach employs more accessible olefinic ynal precursors. In some cases stereoselective reductions of the derived ketone can be used to improve unfavorable diastereomeric ratios as illustrated for **7**/**8** → **11**. Extensions to other ring sizes and experiments with chiral Lewis acid catalysts are currently under investigation.

Acknowledgment. Support for this work by the National Institute of General Medical Sciences of the NIH through Research Grant GM 29475 is gratefully acknowledged. Seeds for the ene-type macrocyclization approach to cembranoids were sown by Dr. K. H. Shulte-Elte during discussions following a seminar by J. A. Marshall at Firmenich (Geneva) on May 19, 1991.

Supplementary Material Available: Experimental procedures for all intermediates and selected ^1H and ^{13}C NMR spectra (44 pages). This material is contained in many 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.

(11) The program MacroModel V 3.1x was employed for these calculations. The TIPS grouping was replaced by *t*-Bu to simplify the calculations. Each structure was subjected to a 1000-step Monte Carlo conformational search in the automated set up mode. For each of the four diastereomers multiple conformers (8-20) were found within 4 kJ of the "global" minimum. Hence, the actual coupling constants are most likely average values. MacroModel V 3.1x was obtained from Professor W. Clark Still to whom we are grateful.

The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement[†,‡]

K. Barry Sharpless,* Willi Amberg, Youssef L. Bennani, Gerard A. Crispino, Jens Hartung, Kyu-Sung Jeong, Hoi-Lun Kwong, Kouhei Morikawa, Zhi-Min Wang, Daqiang Xu, and Xiu-Lian Zhang

Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037

Received March 16, 1992

Summary: Two key improvements in the osmium-catalyzed asymmetric dihydroxylation have led to a simple procedure which is applicable to a wide range of olefins.

The catalytic asymmetric dihydroxylation (AD) of olefins (Scheme I)[1] has been improved steadily during the

[†] Dedicated to Professor Robert H. Grubbs on the occasion of his 50th birthday.

[‡] Both the phthalazine ligand class and the sulfonamide effect were discovered in the Chemistry Department of the Massachusetts Institute of Technology during our final months there in mid-1991.

(1) Two comments on conventions from our earlier papers[2] on this subject: (1) ADH has been abbreviated further to AD and (2) the face selection scheme of the earlier reports (i.e., top/bottom attack) won out over the scheme in our last paper,[2g] which entailed bottom/bottom attack and required flipping the olefin (but also note that the steric blocking features of the mnemonic in ref 2g have been added to the present scheme).

0022-3263/92/1957-2768$03.00/0