Table III. Reactions of 1,5-Bis(bromomagnesio)hexane with Carboxylic Acid Esters in THF Diastereoisomer Distribution

	2-methyl-1-substituted-cyclohexanols[a,b]		
ester, R	yield (%)	*cis*-OH	*trans*-OH
3, H	**21** 57	30	70
4, CH_3	**22** 53	25	75
8, C_6H_5	**23** 54	25	75

[a] Isolated product. [b] Ratios of diastereomers determined by GC and ^1H NMR.

from previous studies of organometallic reactions of 2-methyl-cycloalkanones greatly facilitated this aspect of the study. Pertinent ^{13}C NMR shifts of the methyl and the carbinol carbons, listed in Table II, show that this method readily distinguishes the cis from the trans isomers. The methyl carbon signals of the later consistently appear about 4 ppm downfield from those of the cis diastereoisomers. The carbinol carbon signals are less susceptible to changes in structure but in general the shifts for the cis cyclopentanols have lower values than the trans isomers. In the ^1H NMR spectra the protons of the methyl groups in the trans isomers invariably appear the further upfield, while the results of gas chromatography and flash chromatography show the cis-substituted cyclopentanols to have shorter retention times than the trans alcohols. These methods permitted the ready identification of the products and the relative ratio of the diastereoisomers.

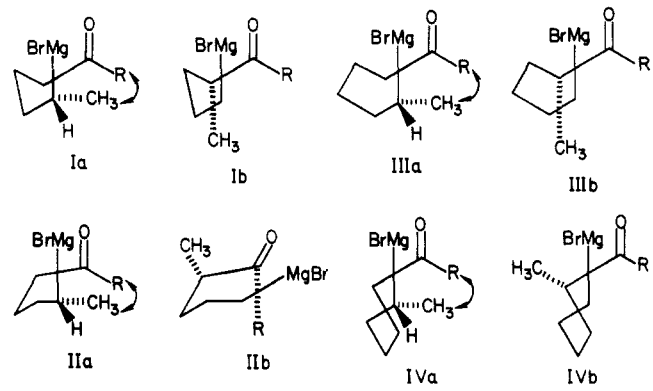
The diastereoselectivity of these reactions must reside in the cyclization step, the second nucleophilic attack of the 5-oxoalkyl Grignard reagent (Scheme II). Since the primary or the secondary Grignard may be responsible for the first reaction with the ester carbonyl, two intermediates, a and b, are possible.

Significantly lower yields of the cyclized products were obtained when 1,5-bis(bromomagnesio)hexane (**2**) was reacted with some of the same esters (**3**, **4**, and **8**). Analysis of the products showed that in the six-membered cyclization, in contrast to the five-membered, competitive inter- and intramolecular processes became relatively important. While the 2-methyl-1-substituted cyclohexanols were isolated in only 53% to 57% yield, the trans diastereoisomers were still greatly favored over the cis (Table III).

At the moment of cyclization, several conformations leading to 2-methyl-1-substituted-cyclopentanols are possible (Ia, Ib, IIa and IIb, Scheme III). In both Ia and IIa there are important steric interactions between the methyl group originating in the reagent and the R group from the original ester. The expected greater reactivity of the secondary center of the di-Grignard reagent suggests that the favored intermediates should be Ib and IIb. The same argument leads to the intermediacy of conformations IIIb and IVb to explain the diastereoselection in the six-membered annelations.

Currently we are undertaking experiments to determine conclusively whether it is the secondary or primary part

Scheme III



of the di-Grignard which initiates the first attack on the ester carbonyl since this information is critical to all discussion concerning the origin of the selectivity.

Registry No. **1**, 63452-95-9; **2**, 101934-18-3; **3**, 109-94-4; **4**, 141-78-6; **5**, 105-37-3; **6**, 5452-75-5; **7**, 3289-28-9; **8**, 93-89-0; **9**, 94-08-6; **10**, 7335-27-5; **11**, 94-30-4; *cis*-**12**, 25144-05-2; *trans*-**12**, 25144-04-1; *cis*-**13**, 16467-04-2; *trans*-**13**, 16467-13-3; *cis*-**14**, 16467-06-4; *trans*-**14**, 16467-12-2; *cis*-**15**, 101934-19-4; *trans*-**15**, 101934-20-7; *cis*-**16**, 22865-13-0; *trans*-**16**, 22862-81-3; *cis*-**17**, 22865-14-1; *trans*-**17**, 22865-01-6; *cis*-**18**, 75968-43-3; *trans*-**18**, 101934-21-8; *cis*-**19**, 75968-45-5; *trans*-**19**, 101934-22-9; *cis*-**20**, 75968-44-4; *trans*-**20**, 101934-23-0; *cis*-**21**, 7443-70-1; *trans*-**21**, 7443-52-9; *cis*-**22**, 19879-11-9; *trans*-**22**, 19879-12-0; *cis*-**23**, 30689-79-3; *trans*-**23**, 30689-80-6; $Br(CH_2)_3CH(CH_3)Br$, 626-87-9; $Br(CH_2)_4CH(CH_3)Br$, 627-96-3.

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Stereoselective Total Synthesis of (±)-Isocelorbicol

Summary: The naturally occurring trihydroxyagarofuran (±)-isocelorbicol (**1**) has been synthesized in 15 steps (3.2%) from 9-keto-α-agarofuran (**2**). This completely stereoselective synthesis includes an osmium tetraoxide oxidation in which the reagent attacks exclusively from the more hindered face of the molecule.

Sir: Isocelorbicol (**1**)[1] is one of a number of complex, polyhydroxylated derivatives of agarofuran which are found in many plants of the family Celastraceae.[2] Although no member of this group of natural products has been shown to possess biological activity, several ester alkaloids based on these sesquiterpenoids have been isolated from *Catha edulis* (khat) a stimulant narcotic used in the Middle East and parts of Africa.[3] Isocelorbicol, although one of the more structurally simple members of this group of natural products still presents a considerable

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(2) Smith, R. A. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1977; Vol. 16, pp 215–248. Smith reviews this class of sesquiterpenes and the derived ester alkaloids.

(3) (a) Baxter, R. C.; Crombie, L.; Simmonds, D. J.; Whiting, D. A.; Braenden, O. J.; Szendrei, K. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2965. (b) Crombie, L.; Crombie, W. M. L.; Whiting, D. A.; Szendrei, K. *Ibid.* **1979**, 2976. (c) Baxter, R. C.; Crombie, W. M. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A.; Szendrei, K. *Ibid.* **1979**, 2982.

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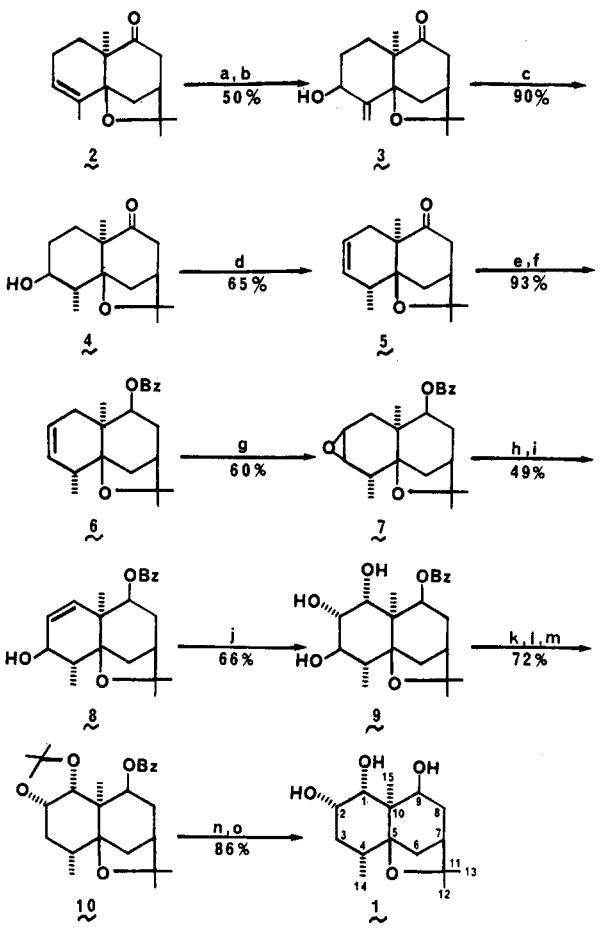
Scheme I[a]



[a] (a) MCPA/CH_2Cl_2/aqueous $NaHCO_3$, 6 h, 25 °C; (b) LDA/ether, 6 h, 25 °C; (c) NH_2NH_2/$NaIO_4$, $CuSO_4$, HOAc, EtOH, 6 h, 25 °C; (d) $POCl_3$/pyridine, reflux, 1 h; (e) $LiAlH_4$/ether/5 h; −50 °C, and then 18 h, 25 °C; (f) BuLi/THF, 10 min, 25 °C, then C_6H_5COCl, 25 °C, 15 min, and then 1 h, 65 °C; (g) MCPA/CH_2Cl_2, 17 h, 25 °C; (h) $(PhSe)_2$/$NaBH_4$/EtOH, reflux, 2 h; (i) MCPA/i-Pr_2NH/CH_2Cl_2, 1 h, −78 °C; (j) OsO_4/pyridine, 25 °C, 16 h; (k) 2,2-dimethoxypropane, CSA, 4 h, 50 °C; (l) NaH, THF, imidazole, 2 h, 60 °C, and then CS_2, 1 h, 50 °C, followed by MeI, 30 min, 25 °C; (m) n-Bu_3SnH, toluene, 18 h, reflux; (n) $Ba(OH)_2$, MeOH, 6 h, 60 °C; (o) 1 N HCl, THF, 1 h, 25 °C.

challenge in terms of total syntheses, in large part due to the presence of six axial substituents appended to a decahydronaphthalene skeleton. This communication describes a highly regio and stereoselective synthesis of triol **1**[4] employing 9-keto-α-agarofuran (**2**) as the starting material.[5]

The principal challenge in a stereoselective synthesis of **1** is the generation of the correct stereochemistry at C-4 in a compound which has appropriate functionality for the subsequent stereoselective generation of the hydroxyl groups present at C-1, C-2, and C-9.

The most general approach to dihydroagarofurans which have an α-methyl group at C-4 is that of Büchi and Wuest which entails reduction of a β-agarofuran.[6] In order to obtain an appropriately functionalized β-agarofuran, enone **2** was converted to allylic alcohol **3**[7] by, first, buffered peracid oxidation to the β-epoxide[8] and then base-catalyzed isomerization (Scheme I).[9] Diimide reduction[10] of **3** gave a single saturated alcohol in good yield, which was assigned structure **4** on the basis of NMR data.[11] The structure of **4** is such that anti elimination of water proceeded smoothly to afford exclusively enone **5**, in which the olefinic double bond serves as a means of introducing the cis hydroxyls at C-1 and C-2 at a later stage in the synthesis. Not only is the hydroxyl in **4** in a trans diaxial relationship to the 2α proton, but the well-known stability of *trans*-2-octalins relative to the 3-isomers favors the formation of **5**.

Lithium aluminum hydride reduction of **5** gave stereoselectively the axial 9β-ol,[12] which was protected as its benzoate ester (**6**). Peracid oxidation of **6** gave, as expected, epoxide **7** by attack of the reagent from the less hindered β-face of the molecule. Attempted base-catalyzed isomerization of **7** under a variety of conditions led predominently to cleavage of the benzoate ester; however, the same net conversion could be effected by trans-diaxial opening of the epoxide with phenyl selenide anion,[13] following by oxidative elimination to give allylic alcohol **8**.[14]

Although reactions in ring A of agarofuran derivatives generally occur from the less congested β-face, it was hoped that osmylation of **8** might provide sufficient quantities of the desired 1α,2α,3β-triol **9** for the completion of the synthesis. Quite unexpectedly, and in spite of the presence of the axial methyl groups at C-4 and C-10, reaction of **8** with a stoichiometric amount of osmium tetraoxide gave triol **9** *as the exclusive product*.[15] Kishi has presented an empirical rule for the stereochemical course of osmium tetraoxide oxidations which predicts hydroxylation anti to an existing hydroxyl group.[16] Danishefsky has recently suggested a stereoelectronic explanation for these hydroxylations which invokes a species with the allylic oxygen orthogonal to a cationoid carbon.[17] Since osmylation of **8** is proceeding from the more hindered face of the molecule and a cationoid center at C-2 cannot easily adopt an orthogonal relationship with the allylic alcohol, Danishefsky's rationalizations do not appear valid this system.[18]

(4) An earlier total synthesis of **1** suffered from a lack of stereoselectivity and/or poor yields in the introduction of the substituents at C-1, C-2, and C-4. Huffman, J. W.; Desai, R. C.; Hillenbrand, G. F. *J. Org. Chem.* **1984**, *49*, 982.

(5) Ketoagarofuran **2** is available in six steps and 10% overall yield from carvone and ethyl vinyl ketone. Huffman, J. W.; Hillenbrand, G. F. *Tetrahedron Suppl.* **1981**, *9*, 269.

(6) Büchi, G.; Wuest, H. *J. Org. Chem.* **1979**, *44*, 546.

(7) All compounds were purified and characterized by infrared, nuclear magnetic resonance (90 MHz) and mass spectrometry. All compounds gave acceptable elemental analyses, and all yields cited are for isolated, purified material.

(8) Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267. Epoxidation of **2** under unbuffered conditions gave poor yields of epoxide, apparently due to competing Baeyer–Villiger oxidation.

(9) Crandall, J. K.; Apparu, J. *Org. React. (N. Y.)* **1983**, *29*, 345.

(10) Hoffman, J. M.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1245.

(11) In particular the secondary methyl signal appears at δ 1.07 (J = 7.9 Hz). For those compounds in this series with an equatorial (β) methyl group the signal invariably appears at lower field with J = 5.5–6.0 Hz.

(12) Huffman, J. W.; Desai, R. C.; LaPrade, J. E. *J. Org. Chem.* **1983**, *48* 1474.

(13) Sharpless, K. B.; Hauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. This is the only step in the sequence which proceeds in less than 60% yield (56%); however, some epoxide **7** is invariably recovered to give a net conversion of 70%.

(14) Reich, H. J.; Wallowitz, S.; Trend, J. E.; Chow, F.; Wendleborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697. In the absence of diisopropyamine oxidation of the phenyl selenide derived from **7** affords lower yields of **8**.

(15) The stereochemistry was initially assigned on the basis of the NMR spectrum of **9** in which the secondary methyl signal is shifted downfield 0.25 ppm relative to that in **8**. Examination of models indicates that *both* faces of the molecule are quite hindered but that the α-face is more congested than the β, due to the presence of the two axial methyl groups.

(16) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Goldsmith, D. J.; Sakano, I. *J. Org. Chem.* **1976**, *41*, 2095. Goldsmith and Sakano also discuss the stereochemical of osmylations in terms of steric effects.

(17) Danishefsky, S. J.; Larron, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.

Kishi's examples are, with one exception, conformationally mobile acyclic systems, and it is suggested that in cyclic systems the effect of an allylic methyl group is similar to that of a hydroxyl substituent.[16] We believe that the overriding factor governing the course of the osmium tetraoxide oxidation of 8 is the stereoelectronic effect of the quasi-axial allylic alcohol which directs hydroxylation anti to the hydroxyl group. Application of this hypothesis to the systems described by both Kishi[16] and Danishefsky,[17] assuming normal ground-state geometry, gives results which are consistent with those obtained by both authors.[19] Prior to removal of the now unnecessary 3β-hydroxyl group, the 1α,2α-diol was protected as the acetonide. Barton deoxygenation[20] proceeded smoothly to afford **10**, which gave racemic **1**, mp 240–241 °C, on removal of the protecting groups. The NMR, solution IR, and mass spectra of synthetic isocelorbicol were identical with those of the natural product.

This synthesis of (±)-isocelorbicol (**1**) from ketoagarofuran **2** entails 15 steps and proceeds in an overall yield of 3.2% with complete stereoselectivity at each step.

Acknowledgment. This work was supported in part by Grant DA-02634 from the National Institute on Drug Abuse. We thank Dr. Cecil R. Smith of the Northern Regional Laboratory, USDA, for copies of the spectra of natural isocelorbicol.

(18) The allylic alcohol in 8 can become orthogonal to a cation at C-2 if ring A is in a half-boat conformation. However, in this conformation the α-face of the double bond suffers severe hindrance from the angular methyl group. Also, the NMR spectrum of 8 clearly indicates that the ground-state conformation is that with ring A in a half chair.

(19) The decreased stereoselectivity described by Kishi (ref 16) for allylic esters is explained by assuming interaction of the unshared electrons of the allylic oxygen with the ester carbonyl.

(20) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

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Reversible Ring-Opening of Thiamine. Kinetic vs. Thermodynamic Control of the Reclosure

Summary: The reversible ring opening and closing of quaternary thiazolium ions (Q^+) is studied, the biphasic behavior observed on reclosure is attributed to N–S acyl transfer, and the results are rationalized in terms of the pH-dependent behavior of the tetrahedral intermediate (T°).

Sir: Various aspects of the chemistry of thiamine (vitamin B_1) are under active investigation.[1] One area which is only partially understood is the reversible ring-opening of the thiazolium ring in aqueous solution[2–4] and its possible role in the transport of thiamine across membranes.[4] Indeed,

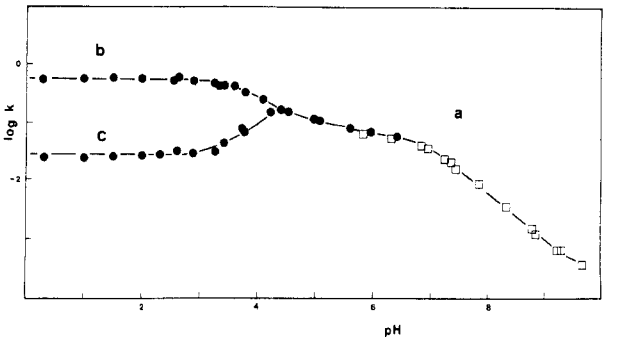
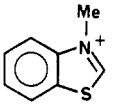


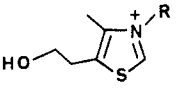
Figure 1. pH–log rate profile for the reclosure of the enethiolate (ETh^-) derived from thiamine ($B1^+$). Units of k are s^{-1}, at 25 °C, I = 1.0 M. Rate constants represented by closed circles were obtained at low buffer strength (0.01 M) by stopped-flow UV spectrophotometry.[5] The open squares are for data obtained by conventional UV measurement of rates extrapolated to zero buffer concentration. The product of processes a and c is thiamine; the product of process b is believed to be the protonated amino thiol ester Es^+. Similar rate profiles have been obtained for reclosure of the thiolates derived from BT^+ and HET^+.

the understanding of this reaction of thiazolium ions in general is relatively limited.

As an approach to these problems we are studying the behavior of thiamine ($B1^+$) and two model ions: the *N*-

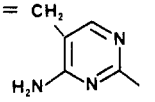


BT^+



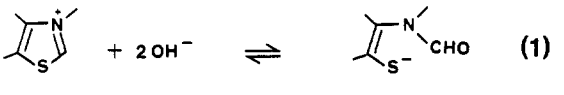
R = Me HET^+

R = CH_2



$B1^+$

methylbenzothiazolium ion (BT^+) and the 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium ion (HET^+), over the whole pH range 0–14 using stopped-flow[5] and conventional UV–vis spectrophotometry. Ring-opening of such quaternary thiazolium ions (Q^+) in basic solution produces amido enethiolates (ETh^-, eq 1), which reclose upon acidifica-



(1)

tion.[2–4] For the equilibrium shown in eq 1 we can define a constant $K^2_{op} = [ETh^-][H^+]^2/[Q^+]$ such that pK_{op} is the pH at which Q^+ and ETh^- are present in equal amounts.[2–4] We now find that reclosure of the enethiolates derived from thiamine and the two model ions at pH < pK_{op} shows one kinetic phase at intermediate pHs but that at low pHs *two* distinct phases are observable.[6]

(1) *Thiamine. Twenty Years of Progress*; Sable, H. Z., Gubler, C. J., Eds.; N.Y. Acad. Sci.: New York, 1982. (*Ann. N.Y. Acad. Sci.* **1982**, *378*, 7–122).

(2) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1, and references cited therein.

(3) (a) Zoltewicz, J. A.; Uray, G. *J. Org. Chem.* **1980**, *45*, 2104. (b) Kluger, R.; Chin, J.; Smyth, T. *J. Am. Chem. Soc.* **1981**, *103*, 884. (c) Hopmann, R. F. W. *Ann. N.Y. Acad. Sci.* **1982**, *378*, 32. (d) El Hage Chahine, J. M.; Dubois, J. E. *J. Am. Chem. Soc.* **1983**, *105*, 2335.

(4) Haake, P.; Duclos, J. M. *Tetrahedron Lett.* **1970**, 461. Duclos, J. M.; Haake, P. *Biochemistry* **1974**, *13*, 5358.

(5) Cf. Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219.

(6) After the inception of the present work two kinetic phases were noted by others[3d] but they were not studied in detail. Surprisingly, the two phases were not noted by Hopmann.[3c]

(7) In addition to the behavior described in the text, the three systems show very similar rates for the plateau regions of processes b and c, as well as similar activation parameters.

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