Table I. ^{13}C NMR Chemical Shifts of Vinyl Cations 3 and 5 and Their Precursors 2 and 4[a]

compd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
2	186.35	103.53	70.10	29.98		80.66	7.81	
3	202.66	111.72	228.92	27.18	30.62	63.66	39.63	
4[b]	197.92	99.01	69.01	29.51		97.86	20.10	
5[b]	245.39	113.97	257.64	32.43	36.44	101.55	16.29	

[a] Compounds 2 and 4 in $CDCl_3$ (77.0 ppm); 3 and 5 referenced to capillary CD_3COCl (δ_{CD_3} = 32.90 ppm); specific assignment of C_4 and C_5 in 3 and 5 tentatively analogous to allyl cations. [b] Reference 1.

vinyl cation by 14 kcal/mol more than two β-methyl groups[6] do.

In 3 the two methyl groups at C_3 are nonequivalent as in other allyl cations.[13] The observed smaller downfield shifts, compared to the precursor, reflect less need for hyperconjugative stabilization from these methyl groups due to less positive charge at C_3 in 3 as compared to 5. Electron donation from the cyclopropyl ring at C_1 decreases electron density at C_3, thus leading to less deshielding for this carbon than that in 5. C_1 is 31 ppm upfield from that in 5 even if a 12-ppm correction for the different shift in the precursors is taken into account.

Charge delocalization away from C_1 and C_3 into the β positions C_7 and C_8 of the cyclopropyl ring is indicated by the shift of the signals for these carbons (39.63 ppm), which is 32 ppm downfield from the precursor. This downfield shift for the β-cyclopropyl carbons is of similar magnitude to that in α-cyclopropyl-stabilized allyl cations,[13] whereas the α-cyclopropyl carbon C_6 in 3 cannot be compared because it is unique to this type of vinyl cation.

At first glance, the upfield shift for the unsaturated cyclopropyl carbon C_6 from 80.66 ppm in 2 to 63.66 ppm in 3 is surprising. In α-cyclopropyl-substituted trigonal cations[13] and also in α-cyclopropyl-substituted vinyl cations,[14] both C_α and C_β ring carbons exhibit considerable downfield shift. The unusual shift for C_6 in 3 may be related to the unusual shift in 2, where C_6 is both terminal allenic and part of a cyclopropyl ring.

The shift of C_6 may also be rationalized by taking into account the unique structure of cyclopropylidenemethyl cations 1, which can be looked upon as the unsaturated analogues of cyclopropylcarbinyl cations. In valence bond terminology there is a difference between 1 and α-cyclopropylcarbinyl cations in that the resonance structures of 1 include homopropargylic cation resonance forms (which of course would be given very unequal weights) whereas cyclopropylcarbinyl resonance structures would be homoallylic. In 3 this would partially change the bond between C_6 and C_1 to a triple bond, giving C_6 some sp character. Calculations on 1 show the C_α–C_β distance became significantly shorter than that of a double bond.[6] In 3 the mutual shielding of the two sp carbons C_6 and C_1 might give rise to the substantial upfield shifts observed for these carbons.

Alternatively, the upfield shift for C_6 in 3 could be explained by polarization effects. The β carbons of vinyl cations are negatively charged,[15] but preliminary calculations for model cations of type 1 and 3 do not show significant differences from 5.[16]

The ^{13}C NMR spectroscopic data of 3 presented here show the first direct experimental proof obtained for a stable vinyl cation in solution utilizing the unique and unusually effective stabilization of such a cation by a β-cyclopropyl ring. These data are in agreement with theory and give additional support to the interpretation of the solvolytic studies of these systems.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft.

Registry No. 3, 88295-38-9.

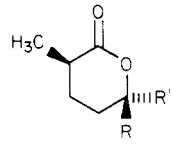
Hans-Ullrich Siehl,* Ernst-Wilhelm Koch
Institut für Organische Chemie
der Universität Tübingen
D-7400 Tübingen 1, West Germany
Received October 24, 1983

(14) Siehl, H.-U., unpublished results.
(15) Apeloig, Y.; Schleyer, P. v. R.; Pople, J. A. *J. Org. Chem.* **1977**, *42*, 3004.
(16) Apeloig, Y., personal communication.

A Convergent Asymmetric Synthesis of (-)-Malyngolide and Its Three Stereoisomers

Summary: (-)-Malyngolide, an antibiotic of algal origin, and its stereoisomers (+)-malyngolide and (+)- and (-)-epimalyngolide have been synthesized asymmetrically in high diastereomeric and enantiomeric purity.

Sir: Since the antibiotic (-)-malyngolide (1) was isolated from marine algae and its structure, including relative and absolute configuration, established in 1979,[1] a number of syntheses[2-5] have been reported. The majority of these lack stereoselectivity, the product being a mixture of (±)-malyngolide and its diastereomer, (±)-epimalyngolide (2), which can be separated by chromatography.[3] One



1, R = n-C_9H_{19}; R' = CH_2OH
2, R = CH_2OH; R' = n-C_9H_{19}

synthesis[4] produces racemic malyngolide stereoselectively and two others produce a mixture of (-)-malyngolide and (+)-epimalyngolide, either by total asymmetric synthesis[5a] or by derivation from a chiral starting material, D-glucose.[5b] We report here a convergent asymmetric synthesis in which either chiral center is produced in one or the other of the two possible configurations. In this way, not only (-)-malyngolide and (+)-epimalyngolide but also their enantiomers were produced in high diastereomeric and enantiomeric purity.

(1) Cardllina, J. H., II; Moore, R. E.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1979**, *44*, 4039.
(2) Babler, J. H.; Invergo, B. J.; Sarussi, S. J. *J. Org. Chem.* **1980**, *45*, 4241.
(3) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1981**, *46*, 2439. Torii, S.; Inokuchi, T.; Yoritaka, K. *Ibid.* **1981**, *46*, 5030. Matsuo, K.; Kinuta, T.; Tanaka, K. *Chem. Pharm. Bull.* **1981** *29*, 3047. Kim, S.; Hong, C. Y.; Moon, Y. C. *J. Org. Chem.* **1982**, *47*, 4350. Kozikowski, A. P.; Nieduzak T. R.; Scripko, J. *Organometallics* **1982**, *1*, 675.
(4) Matsuo, K.; Tanaka, K. *Chem. Pharm. Bull.* **1981**, *29*, 3070.
(5) (a) Sakito, Y.; Tanaka, S.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 1223. (b) Pougny, J.-R.; Rollin, P.; Sinaÿ, P. *Tetrahedron Lett.* **1982**, *23*, 4929. (Separation of epimers was effected at a precursor stage.)

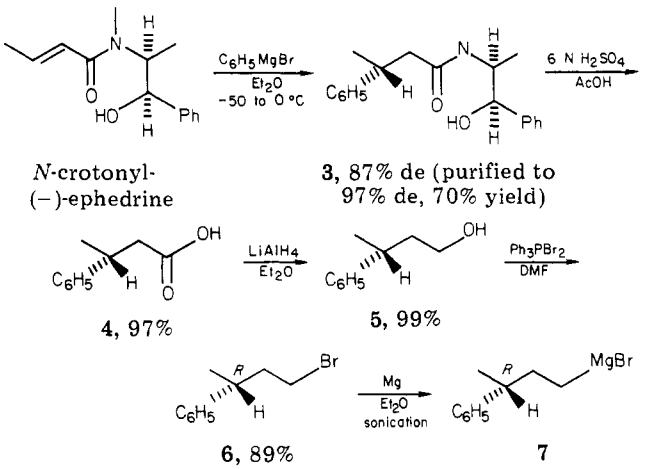
0022-3263/84/1949-0576$01.50/0

Table I. Summary of Reactions in Schemes IV and V

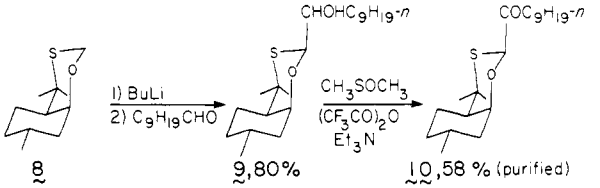
reaction	config; de,[a] %	$[\alpha]^{20}_D$ of 14, deg	product; $[\alpha]^{20}_D$, deg	yield,[b] %
(*R*)-**7** + **10**	2*R*,5*S*; 98	−8.95	malyngolide; −13.4	34
(*R*)-**7** + **12**	2*R*,5*R*; 78	−4.93	epi-5-malyngolide; −20.8	25
(*S*)-**7** + **10**	2*S*,5*S*; 95	+4.63	epi-2-malyngolide; +21.2	38
(*S*)-**7** + **12**	2*S*,5*R*; 95	+8.92	enantiomalyngolide; +12.4	37

[a] Of product **13** or its diastereomers, by proton NMR. [b] Overall, from **10** or **12**.

Scheme I



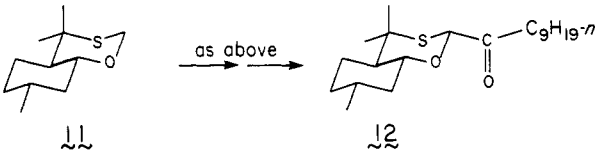
Scheme II



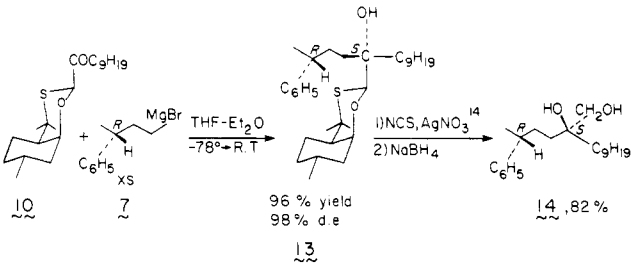
Since malyngolide is a δ-lactone, the corresponding δ-hydroxy acid was chosen as a synthetic target. A phenyl ring was used as the synthon for the carboxylic acid group, and the "upper" part of the molecule was asymmetrically synthesized by a method described (up to **4**) by Mukaiyama[6] and shown in Scheme I. Since the chiral auxiliary reagent in this part of the synthesis is ephedrine, which is readily available in both enantiomerically pure forms, both enantiomers of **6** were accessible. By recrystallizing the 1,4-addition product **3** once, diastereomeric purity[7] was raised from 87% to 97%, and this is presumably the enantiomeric purity of **6**, which was obtained in 59% overall yield from *N*-crotonylephedrine. The elaboration of **4** into **7** (Scheme I) follows standard procedure.

The "lower" part of the molecule was synthesized as shown in Scheme II. Oxathiane **8**[9] is obtained as a by-product in the already published[10] synthesis of its diastereomer **11**. Lithiation reaction with *n*-decanal and oxidation by the Swern method,[11] as previously described, converted **8** to the purified ketone **10** in 46% yield.[12] The

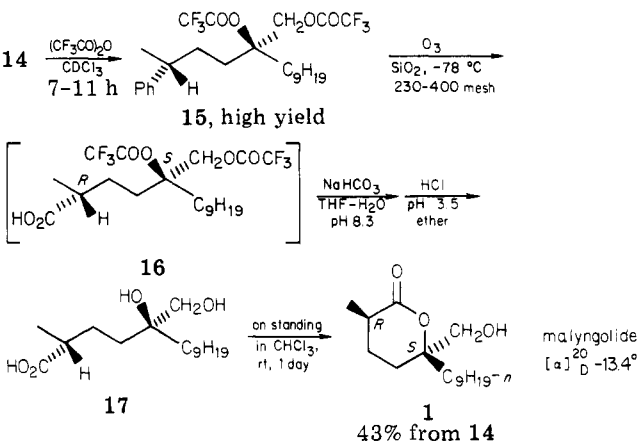
Scheme III



Scheme IV



Scheme V



diastereomer **12** of compound **10** was analogously prepared from oxathiane **11**, as summarized in Scheme III. It should be noted that the oxathiane moieties of **10** and **12** are mirror images.

Combination of **7** and **10** (or **12**) in a highly stereoselective way follows the methodology previously developed.[9,10,13] The course of reaction is shown for **10** in Scheme IV; it is analogous for **12**. Scheme V displays the subsequent steps of the reaction.

The reaction of **10** with either (*R*)-**7** or (*S*)-**7** proceeds with high stereoselectivity (98% by NMR) as shown in Table I. The stereoselectivity in the reaction of **12** with **7** is less, as had been previously observed,[8] 95% d.e. in the reaction with (*S*)-**7** and only 78% in the reaction with (*R*)-**7**, despite the use of $MgBr_2$ as an aid[15] in the latter reaction. (This difference indicates that the distal, benzylic

(6) Mukaiyama and Iwasawa [Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 913] obtained 95% ee.
(7) The estimate of the de of **3** is based on the rotation of **4** reported by: Cram. D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2137. The rotations of **5** and **6** are also reported there. The ee of **3** and **4** in various of our preparations ranged from 96–98%. Direct determination of the de of **3** by NMR is complicated by cis–trans isomerism of the amide bond.
(8) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.
(9) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.*, in press.
(10) Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981**, *22*, 2855.
(11) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(12) This is the yield of analytically pure **10**. Presumably material of somewhat lesser purity could be used in the synthesis.
(13) Eliel, E. L.; Koskimies, J. K.; Lohri, B.; Frazee, W. J.; Morris-Natschke, S.; Lynch, J. E.; Soai, K. *ACS Symp. Ser.* **1982**, *No. 185*, 37.
(14) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(15) Cf.: Eliel, E. L.; Soai, K. *Tetrahedron Lett.* **1981**, *22*, 2859.

chiral center influences the stereoselectivity of the Grignard addition.) Adduct **13** and its stereoisomers were cleaved[14] and reduced to **14** and its stereoisomers as previously described.[8,9]

Ozonization of the phenyl group (Scheme V) required prior protection of the hydroxyl functions in **14** by trifluoroacetylation to **15**. No epimerization at the tertiary carbinol center occurred in this process, in as much as **15** could be hydrolyzed back to **14** without overall change. Ozonization of **15** adsorbed on silica gel[16] to acid **16** followed by hydrolysis to **17** and lactonization to (-)-malyngolide proceeded in moderate (36-43%) yield in the various series (cf. Table I).

Malyngolide can be readily distinguished from epimalyngolide by the proton NMR pattern of the CH_2OH group. Malyngolide displays a characteristic AB pattern centered at 3.57 ppm, J = 12 Hz (3.47, 3.67 ppm) whereas epimalyngolide shows a highly degenerate AB pattern with unresolved inner peaks at 3.60 ppm and very small outer peaks, J = 12 Hz. Since the enantiomeric purity of (*R*)-**7** was 96.8% and the reaction **7** + **10** (Scheme IV) was 98% diastereoselective, it may be calculated that the (-)-malyngolide synthesized should be 97.4% diastereomerically pure[17] and 100% enantiomerically pure *provided* no epimerization occurs in the course of the reactions shown in Scheme V. The proton NMR spectrum of (-)-malyngolide indicated about 4% epimalyngolide, which was removed chromatographically. The final product had $[\alpha]^{20}_D$ -13.4° ($CHCl_3$, *c* 2.01) [lit.[1] [α] -13.0°, lit.[5a] [α] -12.3°, lit.[5b] [α] -12.7°], proton NMR spectrum[18] identical with that of the natural product, ^{13}C NMR, mass, and IR spectra as reported.[1]

The combination of (*S*)-**7** and **12** in analogous manner produced (+)-malyngolide, calculated diastereomeric purity 95.5%, enantiomeric purity 99.9%; the proton NMR spectrum indicated 4% epimalyngolide. After purification the malyngolide had $[\alpha]^{20}_D$ +12.4° ($CHCl_3$, *c* 2.02). We believe the slightly low rotation to be due to a nonstereoisomeric impurity.[19] Combination of (*R*)-**7** and **12** was the worst of the four studied, giving (-)-epimalyngolide (5-epimalyngolide) in a calculated diastereomeric purity of only 87.6% (but still 99.8% enantiomerically pure). Proton NMR confirmed the presence of 13% malyngolide, which was, however, readily removed by column chromatography to give pure epimalyngolide, $[\alpha]^{20}_D$ -20.8° ($CHCl_3$, *c* 2.04). In contrast, the combination of (*S*)-**7** and **10** gave very pure (+)-epimalyngolide (2-epimalyngolide), calculated diastereomeric purity 95.4%, enantiomeric purity 100%, found malyngolide content 2%, $[\alpha]^{20}_D$ +21.2° ($CHCl_3$, *c* 2.005) after purification [lit.[5a] [α] +19.1°; lit.[5b] [α] 17°].

Rotations of the unseparated (and therefore diastereomerically impure) intermediates **14** are included in Table I. The high rotation of (2*R*,5*R*)-**14** is evidently not due to high purity but rather to contamination with the higher rotating (2*R*,5*S*) epimer.

Acknowledgment. This work was supported by NSF Grants CHE-7828118 and CHE-8206402 and the donors of the Petroleum Research Fund, administered by the American Chemical Society, to whom we are grateful. We thank Dr. David Harris for recording the NMR spectra.

Tetsuo Kogure, Ernest L. Eliel*
Department of Chemistry
University of North Carolina
Chapel Hill, North Carolina 27514
Received October 31, 1983

(16) Klein, H.; Steinmetz, A. *Tetrahedron Lett.* **1975**, 4249.
(17) This is the expected percentage of malyngolide in the malyngolide-epimalyngolide mixture, *not* the diastereomeric excess.
(18) We thank Professor T. Mukaiyama for supplying us with proton NMR spectra of (-)-malyngolide and (+)-epimalyngolide.
(19) The fact that the calculated and found percentages of epimeric impurities agreed within experimental error in all four cases is an indication that no epimerization and hence no racemization occurred in the course of the synthesis.

Synthesis of 2-(4-Nitroaryl)propionate Esters

Summary: Alkyl 2-chloropropionates react with nitroaromatic compounds on treatment with base to give alkyl 2-(4-nitroaryl)propionates in good yield.

Sir: Only a few methods of effecting nucleophilic aromatic substitution for hydrogen are synthetically useful.[1] Makosza and coworkers reported that nitroarenes are alkylated by certain carbanions bearing leaving groups at the anionic carbon atoms (Scheme I).[2] Although the success of this process is quite dependent on the substrates and reaction conditions, some leaving group-substituted sulfones[2a], nitriles[2b], sulfoxides[2e] phosphine oxides[2c], and phosphonates[2c] were effectively employed as nucleophiles.

We report the alkylation of nitroaromatic compounds by a new class of nucleophiles, α-halocarboxylic esters. Specifically, use of the readily available and relatively inexpensive 2-chloropropionate esters provides access to 2-(4-nitrophenyl)propionates in good yield with high regioselectivity (Scheme II). These reactions do not work well in the NaOH-Me_2SO system frequently used by Makosza[2] but proceed readily in DMF or *N*,*N*-dimethylacetamide (DMAc) using NaH, potassium *tert*-butoxide (PTB), or sodium *tert*-butoxide as base. Substrates, reaction conditions, products, and yields are shown in Table I. In each case only a single isomer was observed and products always resulted from reaction at the unsubstituted 4-position.

A typical procedure consists of dropwise addition of 1 equiv each of ester and arene onto an ice-cold mixture of 2 equiv of base in solvent. The reactions are quite exothermic[3] and occur immediately on mixing the reactants. The rate of reactant addition is adjusted to maintain the desired temperature. After reaction is complete the crude mixture is partitioned between 1 N HCl and diethyl ether. The products are isolated from the ether phase by distillation or chromatography.

Examination of Table I shows that variation of the nitroaromatic ring substituents and variation of the alcohol portion of the esters had little effect on the yields of products. However, the reaction of phenyl 2-chloropropionate with nitrobenzene under the conditions most suitable for the alkyl ester reactions does not give the anticipated arylpropionate product. In a NaH-DMF system this reaction affords only phenyl 2-phenoxy-

(1) For reviews, see: Chupakhin, O. N.; Postouskii, I. Ya. *Uspekhi Khimii* **1976**, *45*, 908. de Boer, Th. J.; Dirkx, I. P. In "The Chemistry of the Nitro and Nitroso Groups"; Fever, H., Ed.; Interscience: New York, 1969; Vol. 1, p 554. Also see: Armillotta, N.; Bartoli, G.; Bosco, M.; Dalpozzo, R. *Synthesis* **1982**, 836 and references cited therein.
(2) (a) Golinski, J.; Makosza, M. *Tetrahedron Lett.* **1978**, *3495*. (b) Makosza, M.; Winiarski, J. *J. Org. Chem.* **1980**, *45*, 1534. (c) Makosza, M.; Golinski, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 451. (d) Makosza, M. *Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod. (Proc.)*, 1st, **1982**, *Issue* 2, 480-490. (e) Makosza, M.; Golinski, J.; Pankowski, J. *Synthesis* **1983**, 40.
(3) The reaction temperature must be kept below about 50 °C so that the thermal runaway reaction between NaH and DMF is avoided. See: Buckley, J.; Webb, R. L.; Laird, T.; Ward, R. J. *Chem. Eng. News* **1982**, *60*, 5.

0022-3263/84/1949-0578$01.50/0