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THE ISOLATION AND STRUCTURE OF TETRANEURIN-A, A NEW PSEUDOGUAIANOLIDE FROM *PARTHENIUM ALPINUM* VAR. TETRANEURIS (COMPOSITAE)

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Abstract—The isolation and structure determination of tetraneurin-A, (**1**), a new pseudoguaianolide from *Parthenium alpinum* var. tetraneuris, are described. Results from a number of hydrogenation experiments involving C-10 and C-11 exocyclic double bonds in pseudoguaianolides are reported.

INTRODUCTION

IN THE course of a general chemical and morphological investigation of the species *Parthenium alpinum* (Family Compositae), we isolated from a collection of plants described as *P. alpinum* var. tetraneuris (Barneby) Rollins four new sesquiterpene lactones, three of which were obtained crystalline and were named tetraneurin-A, -B, and -C. This paper describes the isolation of all the new compounds and presents evidence to support structure **1** for tetraneurin-A.

Isolation and physical properties of tetraneurin-A. Plant material collected in May 1965 and August 1966 near Portland, Colorado, afforded in about 0·01% yield tetraneurin-A (**1**), $C_{17}H_{20}O_6$, m.p. 186–188°, $[\alpha]_D^{22°}$ +3·7. The UV, IR and NMR spectral data indicated that the new compound contained several of the functional groups which are common to most pseudoguaianolides found in *Ambrosia* and *Parthenium* species.[2] For example, the presence of an α,β′-unsaturated γ-lactone ring in tetraneurin-A was evident from the following data: λ_{max} 210 nm, ε 9670; IR bands at 1730 (carbonyls) and 1640 (double bond) cm^{-1}; and NMR signals which are typical for protons associated with a lactone function (Table 1). The presence of a keto group in a 5-membered carbocyclic ring was suggested by the intensity of the 1730 cm^{-1} IR band and the weak (ε 30) UV absorption near 285–290 nm. An IR band at 3510 cm^{-1} could be ascribed to a tertiary OH group.

Although the NMR spectrum of tetraneurin-A displayed a singlet at 1·05 ppm* typical for a C-5 tertiary Me group, a signal for a C-10 Me group was missing. Instead, the spectrum exhibited some complex signals between 4·0 and 4·6 ppm which corresponded to two overlapping one-proton double doublets; these signals could be attributed to the presence of a CH_2-OAc group attached to an asymmetric C atom since a signal was also observed for an acetyl Me group.

When the spectral results were considered together with the structures of other pseudoguaianolides known to be elaborated by *Parthenium* species,[2] structure **1** was an obvious possibility for tetraneurin-A. That structure **1** did indeed represent

* All chemical shift values are reported in ppm (δ-scale).

TABLE 1. NMR OF TETRANEURIN-A AND RELATED COMPOUNDS[a]

Compd.	H_6	H_7	C_{11}=CH_2	$C_{10}CH_2O$—	C_{10}=CH_2	C_5—Me	C_{10}Me	C_{11}Me	Misc.
1	4·90 d(8)	3·4 c	5·63 d(2) 6·26 d(2·5)	4·0–4·6 c[c]		1·05			2·06 for C_{12}OAc
3[b]	44·8 d(8)	3·44 c	5·58 d(2) 6·23 d(2·5)	3·2–4·0 c[c]		1·01			
4	4·84 d(8)	3·37 c	5·60 d(2) 6·21 d(2)	3·8–4·5 c[c]		0·91			2·47 for *p*-CH_3 from C-12 Ts. 7·37 d(8·5) 7·81 d(8·5) for C_{12}-Ts
5	4·82 d(8)	3·42 c	5·6 d(2) 6·21 d(2)		5·07 d(4·5)	0·95			
6	5·39 d(2)					0·81	1·08 d(7)	1·79 d(1·5)	
9	4·65 d(5)					1·11	1·15 d(6)[d]	1·12 d(6)[d]	
10	4·89 d(7·5)					1·13	1·18 d(6)	1·28 d(6)	
11	4·48 d(8)	3·4 c	5·55 d(3) 6·27 d(3·5)	3·9–4·3 c[c]		1·19			6·13 c for H_2;[e] 2·05 for C_{12}–OAc; 2·9–3·15 c for two H's at C_3

[a] Spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer. Values are given in parts per million relative to tetramethylsilane as an internal standard. Numbers in parentheses denote coupling constants in c/s. Singlets are unmarked; multiplets are described as follows: d = doublet, dd = double doublet, c = complex signal whose center or range is given.

[b] NMR determined for the C-10 CH_2O-trimethylsilyl ether. [See T. J. Mabry, J. Kagan and H. Rösler, *Phytochemistry* **4**, 177 (1965) for the procedure for the preparation of the TMS ether].

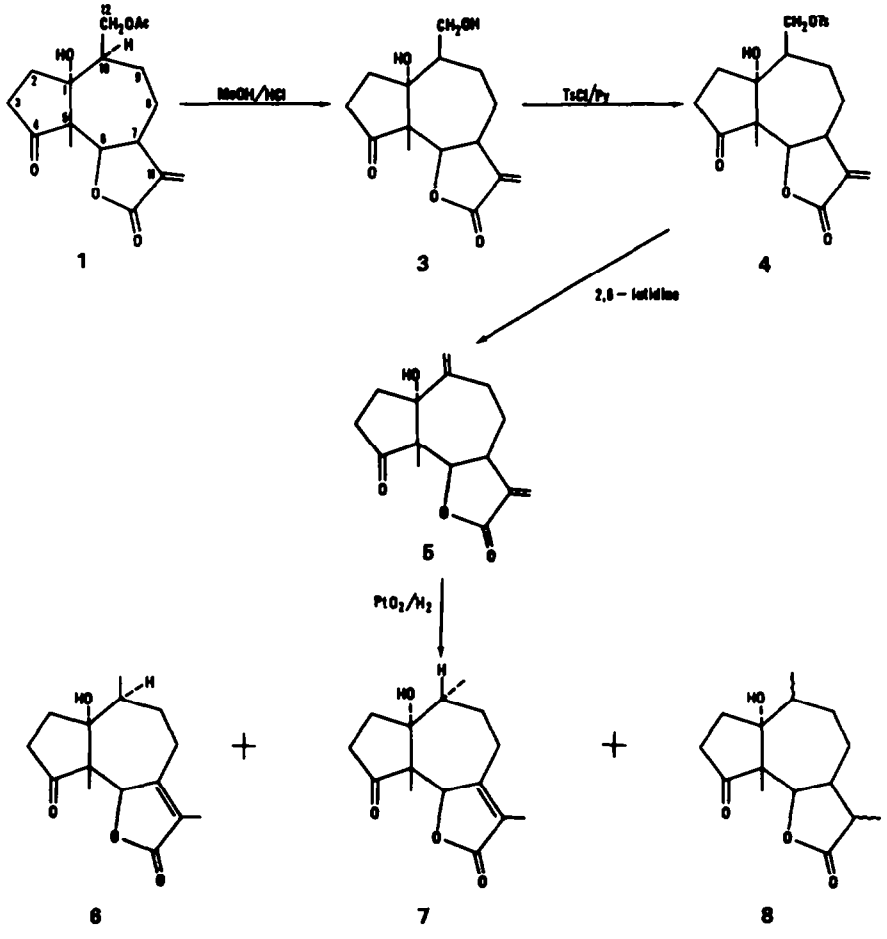
[c] The pattern for these complex signals appeared to correspond to two one-proton double doublets.

[d] The signals for the C-10 and C-11 Me groups overlap, and the present assignments are tentative.

[e] This signal appeared to be two overlapping doublets, J = about 2·5 c/s.

tetraneurin-A was established by first eliminating the C-12 acetoxyl function and then converting the diene thus obtained to substances derived directly from coronopilin[3] (2).

Conversion of tetraneurin-A to isocoronopilin. Tetraneurin-A was readily hydrolyzed with methanolic hydrochloric acid to the diol **3**, $C_{15}H_{20}O_5$, m.p. 246–249°. Treatment of the diol with *p*-toluenesulfonyl chloride afforded a tosylate (**4**), $C_{12}H_{26}O_7S$, m.p. 180–181·5°. Compound **4** was converted to the diene **5**, $C_{15}H_{18}O_4$, m.p. 204–205°, during reflux with 2,6-lutidine. When the diene **5** was hydrogenated in the presence of PtO_2* in a 50 : 1 substrate/catalyst ratio, isocoronopilin (**6**) was obtained in 63% yield. On the basis of the NMR spectrum recorded for the crude reaction



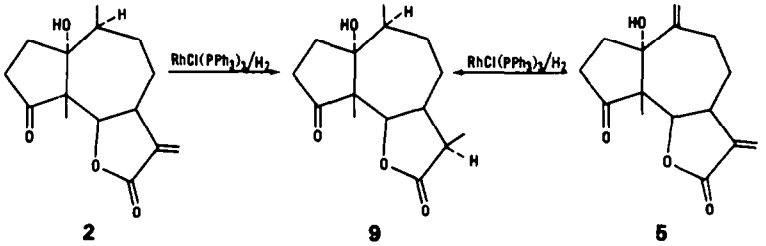
mixture, the remaining material appeared to be **7**, the C-10 epimer of isocoronopilin, and several tetrahydro products (represented by **8**). The best sample of the isocoronopilin from tetraneurin-A melted at 197–198·5° while authentic isocoronopilin (from coronopilin) melted at 201–202·5°; mixed m.p., 200–201°. The synthetic isocoronopilin was identical with the authentic sample by IR, NMR and ORD spectra.

* PtO_2 is preferred to Pd–C as the catalyst for hydrogenation when the least thermodynamically stable product is desired. In addition, a high substrate to catalyst ratio favors the formation of a single product.[4]

The conversion of tetraneurin-A to isocoronopilin established all of the structural features shown in **1** with the exception of the configuration at C-7 and C-10.

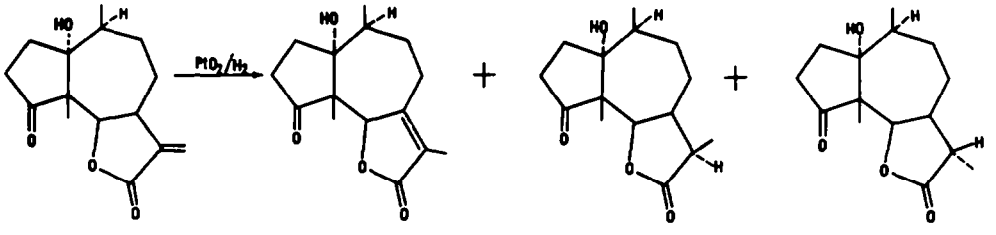
The conversion of tetraneurin-A to dihydrocoronopilin. Since the conversion of tetraneurin-A to dihydrocoronopilin would establish the configuration at C-7 in tetraneurin-A, the diene **5** was hydrogenated in the presence of tris-(triphenylphosphine) rhodium chloride,* a reagent reported, with few exceptions, to catalyze the complete hydrogenation of pseudoguaianolides.[5]†

Hydrogenation of either coronopilin (**2**) or the diene **5** in the presence of the rhodium catalyst gave as the major product the low melting form of dihydrocoronopilin (to which we assign structure **9** on the basis of arguments presented below), m.p. 143–144°. The two samples of dihydrocoronopilin were identical by m.p., mixed m.p., and IR, NMR and ORD spectra.



2 **9** **5**

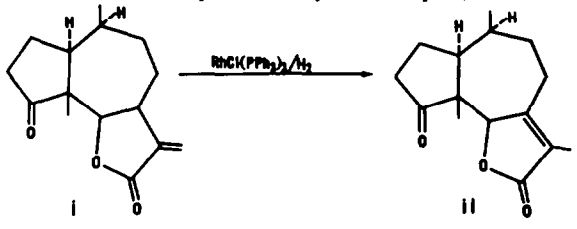
The preparation from coronopilin of isocoronopilin and two epimeric forms of dihydrocoronopilin. Preliminary hydrogenation experiments using 5% Pd-C and PtO_2 as catalysts indicated that almost pure isocoronopilin (**6**) was obtained when a methanolic solution of coronopilin was mixed with the catalyst and then immediately stirred in an atmosphere of hydrogen. When the catalyst was prehydrogenated and a solution containing coronopilin was added slowly to the hydrogenating system,



2 **6** **9** **10**

* The preparation of the rhodium catalyst in all cases was according to a procedure provided by J. Biellmann; the details of the procedure will be described in a forthcoming publication by him.

† Damsin (i) was reported[5] to give mainly isodamsin (ii) when hydrogenated in the presence of the rhodium catalyst. We found that the hydrogenation of damsin in the presence of the rhodium catalyst gave a 3:2 mixture of isodamsin and dihydrodamsin (using the same preparation of catalyst, coronopilin was converted to a 1:3 mixture of isocoronopilin and dihydrocoronopilin).

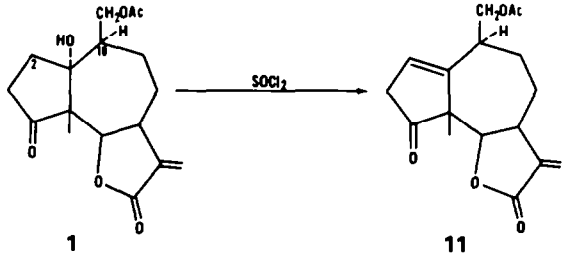


I **II**

isocoronopilin was obtained mixed with two dihydro compounds: **9**, m.p. 143–144° (30% yield) and **10**, m.p. 194–195° (5% yield). The structure assignments for the C-11 epimers of dihydrocoronopilin are based upon the examination of molecular models which suggest that the formation of a beta oriented C-11 methyl group (as in **9**) is favored during the hydrogenation reaction.[6] (The higher melting form, which is designated as **10** here, is the thermodynamically[7] more stable epimer since a 1 : 2 ratio of **9** and **10** was formed when **9** was heated in a methanolic solution of potassium carbonate.)

Reduction of coronopilin with zinc/acetic acid was previously reported to yield only the higher melting epimer,[7] a form which was also recently found to be a constituent of *Hymenoclea salsola* T. and G.[8]

The configuration at C-10 *in tetraneurin-A.* The C-10 CH_2OAc function in tetraneurin-A can be assigned a beta configuration for the following reason. If the C-10 H atom were beta and thus trans to the C-1 OH group, which is known to be alpha, dehydration of tetraneurin-A with thionyl chloride could be expected to produce a double bond between C-1 and C-10. However, treatment of tetraneurin-A with thionyl chloride gave a compound which contained (on the basis of its NMR spectrum) a double bond between C-1 and C-2, i.e. structure **11**; NMR: C-2 vinyl proton at 6·13 ppm; complex signals for CH_2OAc function between 3·9 and 4·3 ppm. A similar result was previously observed for coronopilin.[9]



1 11

On the basis of all the evidence presented, tetraneurin-A can be formulated as shown in structure **1**.

EXPERIMENTAL*

Isolation of tetraneurin-A, -B† and -C†. Collections of *Parthenium alpinum* var. tetraneuris (Barneby) Rollins were made about three miles east of Portland, Colorado, on Highway 120 on 7 May 1965‡ and 17 August 1966. A typical isolation procedure is described. The air-dried ground plant material was extracted with chloroform and worked up by the usual procedure.[3c] A thick syrup (11·7 g) was obtained from 2,280 g of whole plant material; the syrup was chromatographed over a silica gel column (8 cm × 55 cm). Elution of the column with ether yielded in the first 600 ml 5 g of a syrup which did not contain sesquiterpene lactone material (monitored by NMR). The next 700 ml of ether contained tetraneurin-C (300 mg, 0·013% yield), m.p. 145°. Elution with another 600 ml of ether yielded approximately 1 g of a syrup which did not contain lactones. The next ether fraction (600 ml) afforded, after recrystallization, tetraneurin-B (338 mg, 0·015% yield), m.p. 194–195·5°; the mother liquors from the tetraneurin-B crystallization appeared to contain (by NMR) another new sesquiterpene lactone; however the latter substance

* All melting points are uncorrected. Analyses were determined by Dr. Alfred Bernhardt, Max-Planck Institut für Kohlenforschung, Mülheim, West Germany.

† The structures of these compounds will be the subject of a future communication.

‡ Voucher No. 240475, The University of Texas Herbarium, Austin, Texas.

has not yet been obtained crystalline. A final ether fraction (500 ml) yielded tetraneurin-A (178 mg, 0·008% yield), m.p. 186–188°, $[\alpha]_D^{24}$ +3·7 (*c* 2·0, MeOH); IR bands (Nujol): 3510 (OH); 1730 (carbonyls) and 1630 (double bond) cm^{-1}. (Found: C, 63·33; H, 6·93. Calc. for $C_{17}H_{22}C_6$: C, 63·34; H, 6·88%).

Hydrolysis of tetraneurin-A (**1**). A soln of 193·6 mg of tetraneurin-A in 5 ml MeOH which contained 7 drops of conc HCl was heated on a steam bath for 20 min. The solvent was removed *in vacuo*; the residue thus obtained was crystallized from MeOH, yield 155·9 mg (92·6%) of **3**, m.p. 146–249°, $[\alpha]_D^{24°}$ −4·6 (*c* 0·64, MeOH); IR bands (Nujol): 3335 (two OH's), 1726 (carbonyls) and 1655 (double bond) cm^{-1}. (Found: C, 64·42; H, 7·32. Calc. for $C_{15}H_{20}O_5$: C, 64·27; H, 7·19%).

Formation of the tosylate of the diol **3**. A soln of 90 mg of **3** and 95 mg of *p*-toluenesulfonyl chloride in 3 ml of anhyd pyridine was allowed to stand at room temp for 14 hr. Water was added to the reaction mixture and the product was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, and after filtering off the salts the solvent was removed. The residue was crystallized from $CHCl_3$:ligroin; yield 110 mg (78·7%) of **4**, m.p. 180–181·5°; $[\alpha]_D^{24°}$ −20·1 (*c* 0·5, MeOH); IR bands (KBr): 1760 and 1744 (carbonyls), 1635, 1600, 1495, 1475, 1452 and 1408 cm^{-1}. (Found: C, 60·55; H, 5·75. Calc. for $C_{12}H_{26}O_7S$: C, 60·81; H, 6·03%).

Elimination of the tosylate group from **4**. A soln of 83 mg of **4** in 2 ml of 2,6-lutidine containing 1 drop of conc HCl was heated under reflux (N_2 atm) for 16·5 hr. Water was added and the soln was acidified with dil HCl. Ether extraction of the aqueous soln yielded, on work-up, a residue which crystallized from $CHCl_3$: ligroin; yield 29 mg (57·7%) of **5**; m.p. 204–205°; IR bands (KBr): 1760 and 1742 (carbonyls); 1659 and 1639 (double bonds) cm^{-1}. (Found: C, 68·96; H, 6·69. Calc. for $C_{15}H_{18}O_4$: C, 68·69; H, 6·91%).

Hydrogenation of the diene **5** *with* PtO_2 *as catalyst*. A soln of 41·3 mg of **5** in 5 ml AcOH was mixed with 1 mg PtO_2 and the mixture was hydrogenated for 2 hr. An NMR spectrum of the material obtained on work-up of reaction mixture indicated a yield of 63% **6**, 27% of the tetrahydro products (represented by **8**) and 10% of **7**, the C-10 epimer of isocoronopilin. The mixture of iso products was separated from the tetrahydro compounds by thick-layer silica gel G chromatography using ether as the developing solvent: yield of **6** and **7**, 16 mg. The mixture of the two iso compounds, **6** and **7**, was recrystallized from $CHCl_3$-ligroin (2:1) until essentially pure **6**, m.p. 196–197°, was obtained. The NMR, IR and ORD spectra for the synthetic isocoronopilin were identical with those obtained for isocoronopilin, m.p. 201–202·5°, prepared from coronopilin. The ORD data* for both samples of isocoronopilin were as follows: (0·027 g in 100 ml of MeOH) $[\alpha]_{400}$ +44°, $[\alpha]_{322·5}$ +311°, $[\alpha]_{290}$ −263, $[\alpha]_{248·5}$ +1451°, $[\alpha]_{240}$ 0° (last reading).

Hydrogenation of the diene **5** *with* $RhCl(PPh_3)_3$ *as catalyst*. A soln of 20 mg of **5** in 10 ml benzene–ethanol (1:1) was hydrogenated for 1·5 hr at room temp and atm press using 20 mg of tris- (triphenylphosphine) rhodium chloride as catalyst. An NMR spectrum of the crude reaction mixture indicated that the reaction had produced **9** in 70% yield. The other material appeared to be a substance which still contained the C-10 exocyclic double bond (20% yield) and isocoronopilin (10% yield). The catalyst was removed by passing the reaction soln over a small column (5 × 0·6 cm) of silica gel G; elution of the column with ether gave (after recrystallization from ether-ligroin) the low melting form of dihydrocoronopilin (designated here as **9**), m.p. 143–144°; mixed m.p. with dihydrocoronopilin, m.p. 143–144°, (prepared by hydrogenation of coronopilin in the presence of the rhodium catalyst) showed no depression. The IR, NMR and ORD spectra for the two samples of dihydrocoronopilin were identical. The ORD data for both the authentic and synthetic dihydrocoronopilin were as follows: (0·0121 g in 100 ml of MeOH) $[\alpha]_{440}$ +66°, $[\alpha]_{312}$ +995°, $[\alpha]_{270}$ −1040°, $[\alpha]_{250}$ −825°, $[\alpha]_{230}$ −1200°, $[\alpha]_{220}$ −600° (last reading).

Hydrogenation of coronopiln (**2**) *with* Pd–C *as catalyst*. About 50 mg of 5% Pd=C was prehydrogenated in MeOH for 1·5 hr. The coronopilin (3·5 g) was dissolved in 40 ml of MeOH and the soln was added to the hydrogenating system during a 2 hr period. An NMR spectrum of the mixture obtained on work-up of the reaction solution indicated a yield of 65% **6**, 30% of the low melting form of dihydrocoronopilin (designated as **9**) and 5% of the C-11 epimer of **9** (represented by **10**). The mixture was separated on a silica gel column (5 × 44 cm). The column was eluted with ether–$CHCl_3$ (9:1). The first 500 ml fraction from the column contained 1·80 g of a mixture of isocoronopilin and the two dihydro products. Recrystallization of the mixture from ether–ligroin afforded 0·593 g of the low melting dihydro product (**9**), m.p. 143–144°; infrared (Nujol): 3410 (OH), 1772 and 1728 (carbonyls) cm^{-1}. The next 1000 ml of eluate yielded 1·18 g of **6**, m.p. 201–202·5°, IR bands (Nujol): 3320 (OH), 1712 (CO) and 1648 (double bond) cm^{-1}. The high melting **10** was not obtained pure from this reaction.

* We thank Dr. D. J. Cox and Mr. Stanley Cernosek, Department of Chemistry, The University of Texas at Austin, for this data.

When coronopilin (dissolved in MeOH) was mixed with some 5% Pd–C catalyst which had not been prehydrogenated and the hydrogenation was then carried out for 1 hr, **6** was formed in better than 95% yield.

Elimination of tertiary hydroxyl group in tetraneurin-A (**1**). Tetraneurin-A (21 mg) in 2 ml of ice-cold pyridine was mixed with 0·5 ml $SOCl_2$; the soln was kept at room temp for 5 min and then taken to dryness *in vacuo*. Water was added to the residue and the soln thus obtained was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4. After filtering off the salts, removal of the solvent yielded a residue which by NMR (Table 1) could be assigned structure **11**. Purification of the material by thick-layer silica gel chromatography did not yield a crystalline compound.

Epimerization[7] *of the low-melting epimer of dihydrocoronopilin* (**9**). A 1 ml soln of MeOH–H_2O (3 : 1) containing 50 mg of the low melting C-11 epimer of **9** and 70 mg of K_2CO_3 was heated on a steam bath for 80 min. An NMR spectrum of the syrup obtained on work-up of the reaction soln indicated a 2:1 mixture of the high-melting **10** and low-melting **9** C-11 epimers of dihydrocoronopilin. Crystallization of the mixture from ether–ligroin yielded 15 mg of pure **10**, m.p. 194–195°, IR (Nujol): 3470 (OH) and 1750 (CO's) cm^{-1}.

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[5] See J. Biellmann and M. J. Jung, *J. Am. Chem. Soc.* **90**, 1673 (1968) for a notable exception.

[6] See N. H. Fischer and T. J. Mabry, *Tetrahedron* **23**, 2529 (1967).

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[b] J. Kagan and H. B. Kagan, *J. Org. Chem.* **33**, 2807 (1968).