(11) (a) Gollnick, K.; Schenck, G. O. In "1,4-Cycloaddition Reactions", Hamer, J., Ed.; Academic Press: New York, 1967; p 296. (b) Rio, G.; Berthelot, J. *Bull. Soc. Chim. Fr.* **1969,** 1664. (c) Demole, E.; Demole, C.; Berthet, D. *Helv. Chim. Acta* **1973,** *56,* 265. (d) Kondo, K.; Matsumoto, M. *Chem. Lett.* **1974,** 701. (e) Kondo, K.; Matsumoto, M. *Tetrahedron Lett.* **1976,** 391. (f) Harirchian, B.; Magnus, P. D. *Synth. Commun.* **1977,** *7,* 119.

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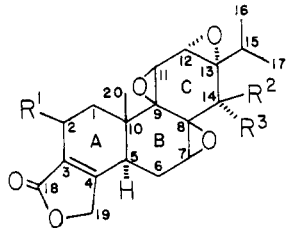
Total Synthesis of Triptolide and Triptonide

Sir:

The isolation of triptolide (**1**), tripdiolide (**2**), and triptonide (**3**) from extracts of *Tripterygium wilfordii* Hook F by Kupchan and co-workers provided the first recognized diterpenoid triepoxides[1] of which **1** and **2** are of special interest owing to their antileukemic activity.[2] Previously we have reported model studies for construction of the C-ring functionality of **3**.[3,4] A synthesis of the C-ring functionality of **1** in a model system has been reported by Koike and Tokoroyama[5] who also claim a synthesis of the A-ring butenolide moiety of **1** from dehydroabietic acid.[6]



1, $R^1 = R^3 = H$, $R^2 = OH$

2, $R^1 = R^2 = OH$, $R^3 = H$

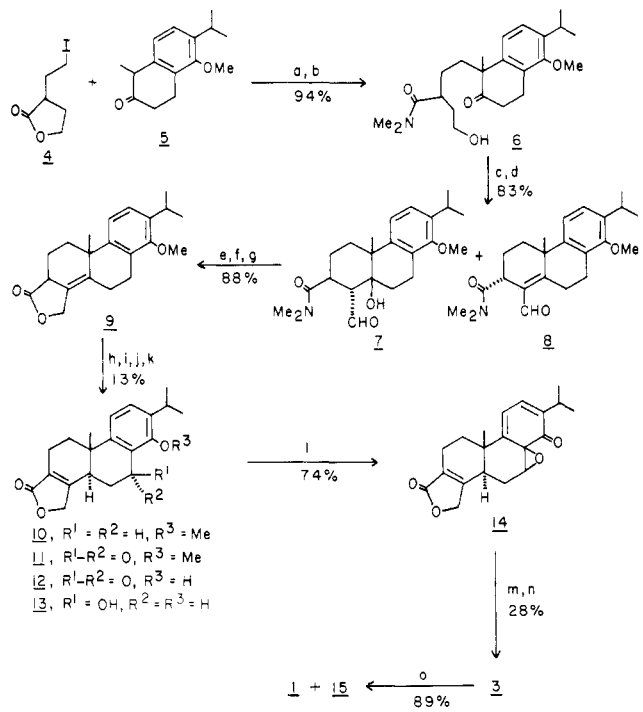
3, $R^1 = H$, R^2–$R^3 = O$

15, $R^1 = R^2 = H$, $R^3 = OH$

We report here the total synthesis of racemic **1** and **3** as outlined in Scheme I. Alkylation of the enolate of **5**[3] with **4** and subsequent cleavage of the lactone with Me_2NH afforded a 1:1 mixture of diastereomers **6**.[7] Oxidation of **6** with CrO_3·py complex gave the diastereomeric aldehydes that underwent Al_2O_3-catalyzed aldol condensation to afford a 1:1 mixture of **7** and **8.** Since cyclization of **6** occurs by approach from the α face of the ketone carbonyl, the stereochemistry of the C-5 hydroxyl group of **7** is β, and the amide and aldehyde groups are trans diequatorial ($J_{H_3-H_4}$ = 10 Hz). Amide **7** originates from one diastereomer of **6** and amide **8** from the other; therefore the amide group of **8** is α as indicated. Although **7** and **8** are readily separated, for further transformation the mixture is treated with acid to effect dehydration of **7,** followed by aldehyde reduction with $NaBH_4$ and acid-catalyzed lactonization during acidic workup, to afford a single isomer assigned structure **9.**[8] Methoxide-catalyzed isomerization of **9** afforded **10.**[8] Benzylic oxidation of **10** gave **11**[8,9] that was demethylated to afford phenol **12.** Reduction of **12** with $NaBH_4$ gave exclusively the C-7β alcohol (**13**),[8] the stereochemistry of which was established as described previously in model studies.[3]

Butenolide **13** was converted into **3** by a sequence similar to that developed previously for construction of the C-ring functionality.[4] Periodate oxidation of **13** afforded epoxy dienone **14.**[8] Epoxidation of **14** with *m*-CPBA gave the β oxide at C-9,11,[10] and subsequent epoxidation with basic H_2O_2 afforded the α oxide at C-12,13 to complete the total synthesis of racemic triptonide (**3**).[11] Borohydride reduction of **3,** as described by Kupchan,[2] afforded triptolide (**1,** 21%)[11] and 14-epitriptolide (**15,** 68%) which were separated by chromatography on silica gel. Although **1** is the minor product from the reduction of **3, 15** can be reoxidized to **3** (CrO_3·py-CH_2Cl_2) in 77% yield.

Scheme I[a]



10, $R^1 = R^2 = H$, $R^3 = Me$
11, R^1–$R^2 = O$, $R^3 = Me$
12, R^1–$R^2 = O$, $R^3 = H$
13, $R^1 = OH$, $R^2 = R^3 = H$

[a] (a) NaH, DMF, 25 °C, 12 h; (b) Me_2NH, 25 °C, 12 h; (c) CrO_3·py, CH_2Cl_2, 25 °C, 15 min; (d) grade 3 neutral alumina, EtOAc, 25 °C, 48 h; (e) *p*-TosOH (catalyst), C_6H_6, reflux, 2 h; (f) $NaBH_4$, EtOH, 25 °C, 2 h; (g) aqueous HCl (workup); (h) MeO^-, MeOH, 25 °C, 15 min; (i) CrO_3, HOAc–H_2O (9:1), 25 °C, 6 h; (j) BBr_3, CH_2Cl_2, 25 °C, 10 h; (k) $NaBH_4$, EtOH, 25 °C, 1 h; (l) $NaIO_4$, aqueous MeOH, 25 °C, 5 h; (m) *m*-CPBA (3 equiv), CH_2Cl_2, 35 °C, 20 h, to 25 °C, 18 h; (n) 30% H_2O_2 (1.75 equiv), 1 N aqueous NaOH (1.3 equiv), MeOH, 25 °C, 20 h; (o) $NaBH_4$, EtOH, 25 °C, 1 h.

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References and Notes

(1) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972,** *94,* 7194–7195. For the isolation of **1** and **3,** see also *K'o Hseuh T'ung Pao,* **1977** *22,* 458–460; *Chem. Abstr.* **1978,** *88,* 77077y.
(2) Kupchan, S. M.; Schubert, R. M. *Science* **1974,** *185,* 791–793.
(3) Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1977,** *42,* 2569–2574.
(4) Frieze, D. M.; Berchtold, G. A.; Blount, J. F. *Tetrahedron Lett.* **1978,** 4607–4610.
(5) Koike, H.; Tokoroyama, T. *Tetrahedron Lett.* **1978,** 4531–4534.
(6) Koike, H.; Tokoroyama, T. *Chem. Lett.* **1979,** 333–336. The data presented by these authors do not exclude the possibility that their product is actually a $\Delta^{4,5}$ isomer rather than the $\Delta^{3,4}$ butenolide.
(7) Satisfactory spectral data have been obtained for all new substances described. Satisfactory analytical data (combustion or high-resolution mass spectrum) have been obtained for all new substances except **13.** High-resolution mass spectra were provided by the facility supported by National Institutes of Health Grant RR00317 (Principal Investigator Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources.
(8) **9:** mp 159–160 °C; IR ($CHCl_3$) 1786, 1770, (CCl_4) 1787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 6 H, J = 7 Hz, $-CHMe_2$), 1.38 (s, 3 H, $-CH_3$), 3.67 (s, 3 H, $-OCH_3$), 4.83 (m, 2 H, $-OCH_2-$), 7.01 (d, 1 H, J = 8 Hz, Ar H), 7.05 (d, 1 H, J = 8 Hz, Ar H). **10:** mp 162–162.5 °C; IR ($CHCl_3$) 1755, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (d, 6 H, J = 7 Hz, $-CHMe_2$), 1.30 (s, $-CH_3$), 3.64 (s, 3 H, $-OCH_3$), 4.75 (m, 2 H, $-OCH_2-$), 7.07 (s, 2 H, Ar H). **11:** mp 180–181 °C; IR ($CHCl_3$) 1752, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3 H, >C–CH_3), 1.24 (d, 3 H, J = 7 Hz, $-CHMe_2$), 1.26 (d, 3 H, J = 7 Hz, $-CHMe_2$), 1.6–3.2 (m, 7 H), 3.42 (septet, 1 H, J = 7 Hz, $-CHMe_2$), 3.86 (s, 3 H, $-OCH_3$), 4.80

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(m, 2 H, $-CH_2O-$), 7.21 (d, 1 H, $J = 8$ Hz, Ar H), 7.52 (d, 1 H, $J = 8$ Hz, Ar H). **13:** mp 127–128 °C; IR ($CHCl_3$) 3580, 3360, 1755, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3 H, $>C-CH_3$), 1.23 (d, 3 H, $J = 7$Hz, $-CHMe_2$), 1.27 (d, 3 H, $J = 7$ Hz, $-CHMe_2$), 1.5–3.2 (m, 7 H), 3.33 (septet, 1 H, $J = 7$ Hz, $-CHMe_2$), 4.78 (m, 2 H, $-CH_2O-$), 5.18 (m, 1 H, $W_{1/2} = 16$ Hz, H–C–OH), 6.87 (d, 1 H, $J = 8$ Hz, Ar H), 7.17 (d, 1 H, $J = 8$ Hz, Ar H). **14:** mp 80–83 °C; IR ($CHCl_3$) 1755, 1680, 1660, 1637, 1582 cm^{-1}; UV (MeOH) 343 nm (ϵ 4954); ^1H NMR ($CDCl_3$) δ 1.10 (d, 6 H, $J = 7$ Hz, $-CHMe_2$), 1.15 (s, 3 H, $>C-CH_3$), 1.5–2.6 (m, 7 H), 2.93 (septet, 1 H, $J = 7$ Hz, $-CHMe_2$), 4.07 (m, 1 H, epoxy H), 4.70 (m, 2 H, $-CH_2-O-$), 6.42 (d, 1 H, $J = 7$ Hz, C_{11} H), 6.99 (d, 1 H, $J = 7$ Hz, C_{12} H).

(9) Ketone **11** and the corresponding isomer with cis A-B ring fusion are each obtained in ~15% yield, and the cis isomer is the more stable isomer. Quinone resulting from oxidation of the aromatic ring is also produced (35%). Separation was effected by column chromatography on silica gel and recrystallization. Efforts to improve the oxidation procedure are in progress.

(10) Bis epoxidation of **14** with *m*-CPBA to afford **3** in one step (22%) has been observed and is under further study.

(11) The structure of racemic **1** (mp 255–256 °C) and **3** (mp 225–226 °C) was established by comparison of spectral data with those of the natural substances. We thank the late Professor S. M. Kupchan for providing IR and ^1H NMR spectral data.

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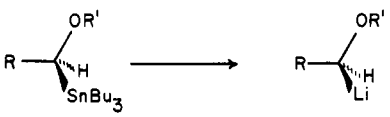
α-Alkoxyorganolithium Reagents. A New Class of Configurationally Stable Carbanions for Organic Synthesis

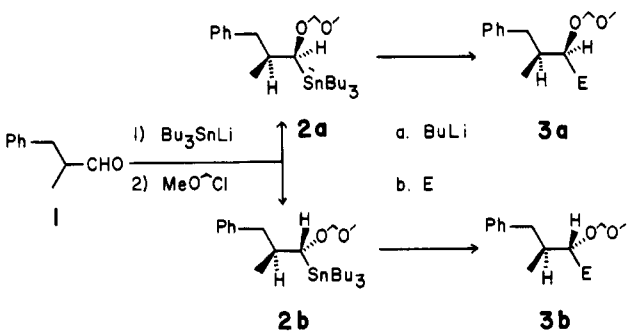
Sir:

Recent preparations of stereochemically defined organolithium reagents have provided a most useful approach to the stereospecific construction of carbon–carbon bonds. These reagents have however been limited largely to vinyl- and cyclopropyllithiums.[1] We report here the preparation of a new class of configurationally stable organolithiums which are sp^3 hybridized, acyclic, and may be obtained as diastereomerically or enantiomerically pure reagents.

Early attempts to prepare chiral organometallics from metals and optically active alkyl halides led to extensively racemized products, a result presumably due to the intermediacy of free radicals on the reaction pathway.[2] Later investigations showed however that the exchange reaction of alkyllithiums with resolved *sec*-butylmercuric chloride proceeded with clean retention of configuration.[3] Although the exchange reported is not a synthetically useful one owing to the presence of other lithium reagents in the product, the experiment did show that sp^3 organolithiums should be configurationally stable once formed. Since α-alkoxyorganolithium reagents may be prepared by a fast, low-temperature exchange from the corresponding organostannanes,[4] we felt that this route to organolithiums should be a stereospecific one.[5]



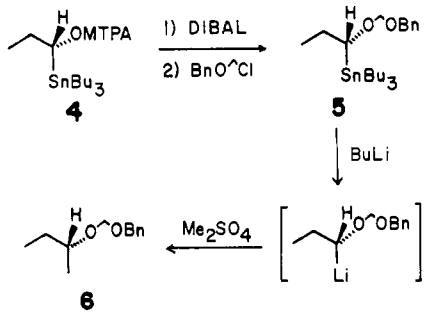
We therefore examined the stereochemistry of the exchange reaction in the following way. 2-Benzylpropanal (**1**) was first treated at −78 °C with tri-*n*-butylstannyllithium (from *n*-Bu_3SnH and $LiNiPr_2$) and then protected with chloromethyl methyl ether (*i*-Pr_2NEt, 0 °C, 1 h) to produce a 1:1 mixture of diastereomers **2a** and **2b** (75% yield). Although the compounds did not resolve on TLC, they could be cleanly separated on a preparative scale by medium-pressure liquid chromatography (MPLC) on silica gel.[6a] Compounds **2a** and **2b** were



then individually treated with *n*-butyllithium (THF, −78 °C) and after 15 min the intermediate α-alkoxyorganolithium reagents were quenched with acetone. Careful high pressure liquid chromatographic (HPLC) examination of the products showed the reactions to be totally stereospecific. Thus **2a** produced a single acetone adduct (90% yield) which was different from the single product afforded by **2b.** These reactions were repeated at −30 °C (THF, 15 min) and again no loss of stereochemistry was observed.[7] Analogous results were obtained with trapping by trimethylchlorosilane.

While the above experiments demonstrate the stereospecific nature of the exchange and trapping, they do not distinguish between retention and inversion. The expected net retention of configuration was verified in one case by trapping the intermediate α-alkoxyorganolithium reagent with a tin halide. Thus, while the lithium reagent prepared from **2a** was unreactive with tri-*n*-butyltin chloride, it did add to tri-*n*-butyltin iodide at −50 °C. The resulting α-alkoxyorganostannane was shown to be the product of retention by its correlation with the starting material, **2a.**

We have also prepared enantiomerically pure α-alkoxyorganolithium reagents from aldehydes by chromatographic resolution of suitable derivatives of the intermediate stannylcarbinols. An example of this operation starts with propanal. Addition of tri-*n*-butylstannyllithium and then esterification with (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(−)-MTPA-Cl][8] gave quantitatively a pair of diastereomeric esters which could be separated by MPLC.[6b,9] The more mobile R[13] ester **4** was converted into the resolved stannylcarbinol by reduction (*i*-Bu_2AlH, $PhCH_3$, −78°C, 90% yield) and was then protected with benzyl chloromethyl ether (*i*-Pr_2NEt, 0 °C, >95% yield) to give **5.** Finally the lithium reagent was prepared as usual (*n*-BuLi, THF, −78 °C) and was alkylated with dimethyl sulfate to yield **6.** Hydrogenolysis (10% Pd/C,



Et_2O) gave optically active 2-butanol. Whereas the (−)-MTPA ester of racemic 2-butanol displayed the carbinol methyl resonances in the NMR ($CDCl_3$) as a pair of doublets at δ 1.25 and 1.33, the (−)-MTPA ester from **6** showed only the lower field doublet.[10] This ester was shown to be identical with that prepared from authentic (*R*)-(−)-2-butanol.

The results described above involve separations of diastereomeric organostannanes as a pathway to stereochemically defined organolithium reagents. Since stereoselective preparations of α-alkoxyorganostannanes would be of considerable value in this area, we briefly examined α induction in the addition of tributylstannyl nucleophiles to several α-substituted

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