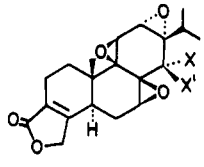
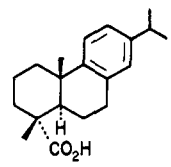
Total Synthesis of *l*-Triptonide and *l*-Triptolide

Sir:

As members of a novel structural class, the diterpene triepoxides, triptolide (**1**) and congeners possess potent cytotoxic—in particular, antileukemic—properties,[1] but unfortunately remain hardly accessible natural products. Herein we describe the total synthesis



1 X=H; X'=OH
2 X,X'=O



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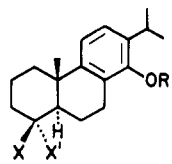
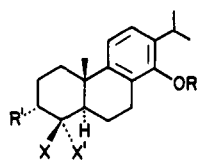
of *l*-triptonide (**2**) and *l*-triptolide[2] by a route utilizing the readily available resin acid *l*-dehydroabietic acid (**3**)[3] as the practical starting material.[4]

In preparation for construction of the lactone moiety, the trifluoroacetate **4** of the known,[5,6] dehydroabietic acid derived, phenol **5** was degraded to ketone **6** by a precedented sequence.[2a,7]



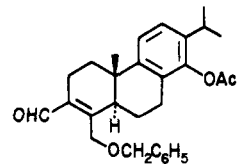
4 R=$COCF_3$; X=CH_3; X'=CO_2H
5 R=H; X=CH_3; X'=CO_2H
6 R=H; X,X'=O
7 R=$COCF_3$; X=CH_3; X'=NCO
8 R=H; X=CH_3; X'=$N(CH_3)_2$
9 R=H; X,X'=CH_2



10 R=H; R'=CH_2OH; X,X'=O
11 R=H; R'=CH_2OH; X=OH; X'=$CH_2OCH_2C_6H_5$
12 R=Ac; R'=CHO; X=OH; X'=$CH_2OCH_2C_6H_5$

Curtius degradation of **4** [(i) $SOCl_2$, benzene–DMF, 50 °C; (ii) NaN_3, H_2O–acetone, 3 °C; (iii) toluene, 100 °C] provided isocyanate **7** (90%), which was converted without purification (50%) to tertiary amine **8** by $LiAlH_4$ in refluxing THF followed by refluxing HCO_2H–aqueous HCHO. After oxidation to the *N*-oxide of **8** (*m*-CPBA, $CHCl_3$, −20 °C), 30-min reflux in $CHCl_3$ effected Cope elimination, giving olefin **9** (80%) as an oil, $[\alpha]^{25}_D$ +214° (*c* 0.06, hexane). Oxidative cleavage (OsO_4–$NaIO_4$, AcOH–dioxane–H_2O, 20 °C) afforded ketone **6** (30%);[8] mp 143–145 °C, $[\alpha]^{20}_D$ +185° (*c* 0.05, $CHCl_3$).

In order to elaborate the butenolide function, intermediate **6** first was transformed (50%; 73% based on starting material consumed) to β-hydroxy ketone **10**[9] [mp 157–159 °C, $[\alpha]^{25}_D$ +121° (*c* 0.025, $CHCl_3$)] by generation of the enolate with $(i\text{-Pr})_2NLi$ followed by its reaction with gaseous HCHO, all in THF at −78 °C. After the alcohol was blocked as the 2-methoxypropyl ether [$MeOC(CH_3)=CH_2$–AcOH, 20 °C], a second, protected methylol unit was appended,[10] giving triol monobenzyl ether **11**[11] by successive treatment with (a) 2 equiv of $PhCH_2OCH_2Li$ (THF, 45 min at −78 °C, then 30 min at −20 °C) and (b) pH 1 hydrochloric acid–THF at 20 °C (70% overall). After formation of the phenolic monoacetate of **11**, through successive exposure to $MeOC(CH_3)=CH_2$–AcOH, Ac_2O–pyridine, and pH 1 hydrochloric acid–MeOH (all at 20 °C), CrO_3–pyridine·HCl oxidation (CH_2Cl_2, 20 °C) yielded (90% overall) aldehyde **12** as an unstable oil. Dehydration to the α,β-unsaturated aldehyde **13**[12]



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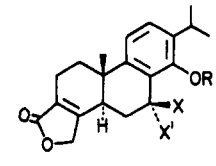

14 R=Ac; X,X'=H
15 R=Ac; X,X'=O
16 R=H; X=OH; X'=H

was managed (20%) by treatment with $o\text{-}C_6H_4(NH_2)_2$–$PhCO_2H$ (EtOH, 20 °C),[13] followed by hydrolysis (pH 1 hydrochloric acid–EtOH, 20 °C) of the presumed intermediary *o*-phenylenediamine imine of **13**. Oxidation of **13** to the carboxylic acid level ($NaClO_2$–$HOSO_2NH_2$, dioxane–H_2O, 20 °C)[14] followed by hydrogenolysis of the benzyloxy group (H_2–Pd–C, EtOH, 20 °C) was concluded by spontaneous lactonization, affording in quantitative yield butenolide **14**.[15]

As a means of access to the triepoxy ketone assemblage in **2**, lactone **14** was initially oxidized[16] (20%) to the oily ketone **15** (CrO_3, AcOH–H_2O, 40 °C), then saponified (KOH, MeOH–H_2O, 20 °C) to the unisolated, free phenol, and finally reduced ($NaBH_4$, EtOH, 20 °C) to the benzyl alcohol **16**[17] (95% from **15**). The prototypic oxidation course described by Adler et al.[18] was applied, as previously,[2b,19] in the conversion ($NaIO_4$, MeOH–H_2O, 20 °C) of phenol **16** to epoxy dienone **17**. The latter, without purification, was treated with H_2O_2–KOH (MeOH,

(1) S. M. Kupchan, W. A. Court, R. G. Dailey, Jr., C. J. Gilmore, and R. F. Bryan, *J. Am. Chem. Soc.*, **94**, 7194 (1972); (b) S. M. Kupchan and R. M. Schubert, *Science (Washington D.C.)*, **185**, 791 (1974).

(2) Previous syntheses of tetracyclic members of this α,β-unsaturated lactone class include: (a) isodehydroabietenolide, E. E. van Tamelen, E. G. Taylor, T. M. Leiden, and A. F. Kreft III, *J. Am. Chem. Soc.*, **101**, 7423 (1979); (b) racemic triptolide and triptonide, R. S. Buckanin, S. J. Chen, D. M. Frieze, F. T. Sher, and G. A. Berchtold, *ibid.*, **102**, 1200 (1980); (c) *l*-stemolide, E. E. van Tamelen and E. G. Taylor, *ibid.*, **102**, 1202 (1980).

(3) Total synthesis: G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 250 (1956).

(4) Practical procedure for isolation: N. J. Halbrook and R. V. Lawrence, *J. Org. Chem.*, **31**, 4246 (1966).

(5) A. Tahara and H. Akita, *Chem. Pharm. Bull.*, **23**, 1976 (1975).

(6) A similar, but improved, route to **5**, to be disclosed elsewhere, has been developed in this laboratory by J. Demers and D. Wolner.

(7) J. W. Huffman and R. F. Stockel, *J. Org. Chem.*, **28**, 506 (1963).

(8) **6**: IR (neat) 3500, 1709, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H, $-CH_3$), 1.26 (d, 6 H, *J* = 7 Hz, $-CHMe_2$), 3.15 (sept, 1 H, *J* = 7 Hz, $-CHMe_2$), 4.75 (s, 1 H, D_2O exch, ArO*H*), 6.88 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.06 (d, 1 H, *J* = 8 Hz, Ar*H*).

(9) **10**: IR (KBr) 3400, 1680, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 3 H, $-CH_3$), 1.25 (d, 6 H, *J* = 7 Hz, $-CHMe_2$), 3.14 (sept, 1 H, *J* = 7 Hz, $-CHMe_2$), 3.85 (m, 2 H, $-CH_2OH$), 4.81 (s, 1 H, D_2O exch, ArO*H*), 6.87 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.06 (d, 1 H, *J* = 8 Hz, Ar*H*).

(10) W. C. Still, *J. Am. Chem. Soc.*, **100**, 1481 (1978).

(11) **11**: IR (neat) 3400, 1455, 1423, 1100, 1027, 910, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 1.25 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 1.35 (s, 3 H, $-CH_3$), 3.14 (sept, 1 H, *J* = 7 Hz, $-CHMe_2$), 3.51 (d, 1 H, *J* = 9 Hz, C_4—CH_2O–), 3.66 (d, 1 H, *J* = 9 Hz, C_4—CH_2O–), 3.4–3.8 (m, 2 H, $-CH_2OH$), 4.56 (s, 2 H, $PhCH_2O$–), 4.63 (s, 1 H, D_2O exch, ArO*H*), 6.81 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.01 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.33 (s, 5 H, *Ph*CH_2O–).

(12) **13**: IR (neat) 1761, 1699, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3 H, $-CH_3$), 1.18 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 1.20 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 2.34 (s, 3 H, $-O_2CCH_3$), 2.90 (sept, 1 H, *J* = 7 Hz, $-CHMe_2$), 4.34 (d, 1 H, *J* = 11 Hz, C_4—CH_2O–), 4.62 (d, 1 H, *J* = 11 Hz, C_4—CH_2O–), 4.55 (s, 2 H, $PhCH_2O$–), 7.12 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.24 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.34 (s, 5 H, *Ph*CH_2O–), 10.14 (s, 1 H, –CHO).

(13) A wide variety of acid and base catalysts for the conversion of **12** to **13** were examined, the specified reagent system affording the purest product, free of the A/B cis isomer.

(14) B. O. Lindgren and T. Nilsson, *Acta Chem. Scand.*, **27**, 888 (1973).

(15) **14**: IR (KBr) 1740, 1190, 1056, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3 H, $-CH_3$), 1.19 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 1.21 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 2.35 (s, 3 H, $-O_2CCH_3$), 2.90 (sept, 1 H, *J* = 7 Hz, $-CHMe_2$), 4.76 (m, 2 H, $-CH_2O$–), 7.15 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.26 (d, 1 H, *J* = 8 Hz, Ar*H*).

(16) R. C. Cambie, L. N. Mander, A. K. Bose, and M. S. Manhas, *Tetrahedron*, **20**, 409 (1964).

(17) **16**: ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H, $-CH_3$), 1.22 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 1.25 (d, 3 H, *J* = 7 Hz, $-CHMe_2$), 3.30 (sept, 1 H, *J* = 7 Hz, $-CHMe_2$), 4.78 (m, 2 H, $-CH_2O$–), 5.25 (br t, 1 H, *J* = 15 Hz, ArC*H*(OH)–), 6.87 (d, 1 H, *J* = 8 Hz, Ar*H*), 7.16 (d, 1 H, *J* = 8 Hz, Ar*H*), 8.03 (br s, 1 H, D_2O exch, ArO*H*).

(18) H.-D. Becker, T. Bremholt, and E. Adler, *Tetrahedron Lett.*, 4205 (1972).

(19) (a) F. T. Sher and G. A. Berchtold, *J. Org. Chem.*, **42**, 2569 (1977). (b) D. M. Frieze, G. A. Berchtold, and J. F. Blount, *Tetrahedron Lett.*, 4607 (1978). (c) For a different method for constructing the polyepoxy ketone moiety of the triptolide family, see: H. Koike and T. Tokoroyama, *ibid.*, 4531 (1978).

(20) Undergraduate student in the Honors Program in Chemistry.

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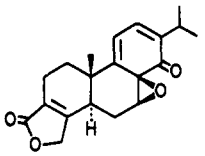

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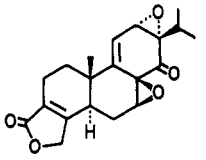

18

20 °C), giving bisoxide **18**, along with the 12,13-β-epoxy isomer. The mixture was immediately further oxidized with 3,5-$(NO_2)_2C_6H_3CO_3H$–Na_2HPO_4 (CH_2Cl_2, 20 °C), forming *l*-triptonide (15% from **17**; mp 251–252 °C) purified by chromatography (Porasil T, EtOAc–hexane). The synthetic material was identical in all respects (IR, NMR, UV, CD; mmp 250–252 °C) with a sample of authentic triptonide. In view of the reported[1,2b] reconstitution of the triptolide system by sodium borohydride reduction of **2**, the above synthesis embraces the former natural product as well.

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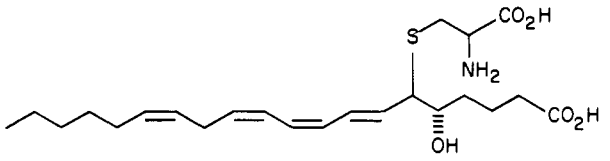
Total Synthesis of (5*S*,6*R*,7*E*,9*E*,11*Z*,14*Z*)-5-Hydroxy-6-[(2*R*)-2-amino-2-(carboxyethyl)thio]-7,9,11,14-eicosatetraenoic Acid, a Potent SRS-A

Sir:

The slow-reacting substance of anaphylaxis (SRS-A) is a highly spasmogenic material and possibly plays an important role in asthma and other diseases of the respiratory system.[1] A structure for the SRS-A had been proposed by Samuelsson et al.[2] as **1** and



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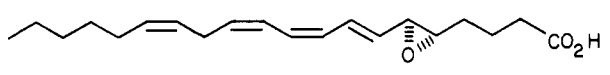
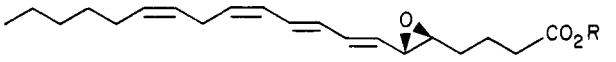


2

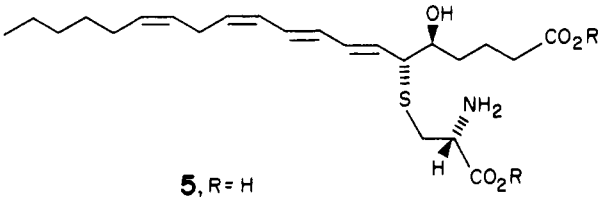
was thought to arise by the addition of cysteine to the epoxide **2**, which is derived from arachidonic acid. Other publications[3,4] suggested that there may be a family of compounds exhibiting SRS-A properties, one member of this group being the product resulting from ring opening of the epoxide **2** by glutathione. Until quite recently, there was still some doubt as to the stereochemical nature of the double bonds in the SRS-A, and while some authors[2] preferred structure **2** for the epoxide, others[5] favored **3**. This



3, R = H
4, R = CH_3

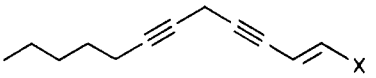
problem has been resolved by the elegant synthesis of the glutathione adduct of **3**, by Corey and his group,[6] which was shown to be the same material as the SRS-A derived from a mouse mast cell tumor line (UV spectrum and high-performance liquid chromatography).

In this communication, we report the synthesis of (5*S*,6*R*)-**5**, a potent spasmogenic agent, via the racemic *trans*-epoxide **4**. As



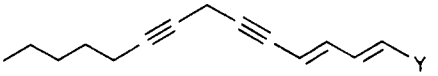
5, R = H
6, R = CH_3

in the case of the recently reported syntheses,[5,18b] our approach also employed a polyene sulfonium salt for the construction of the desired epoxide. The key sulfonium salt **12** was prepared as follows. The copper-catalyzed coupling of 1-bromo-2-octyne[7] with the ethyl vinyl ether adduct of (*E*)-1-hydroxy-2-penten-4-yne[8] gave **7** (EtMgBr, CuCl, THF, 60 °C, 1 h), and subsequently the alcohol

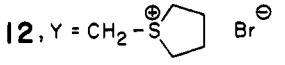


7, X = $CH_2OCH(CH_3)OC_2H_5$
8, X = CH_2OH
9, X = CHO
10, X = $CH(OH)CH{=}CH_2$

8 after acid hydrolysis[9] (acetone, 0.2 N H_2SO_4, room temperature, 3 h, 84% overall yield). Oxidation of this material with pyridinium dichromate[10] (CH_2Cl_2, room temperature, 3 h) gave the aldehyde **9** which was converted to the vinyl carbinol **10** with vinylmagnesium chloride (THF, −40 °C, 30 min, 58% from **8**). Exposure of **10** to phosphorus tribromide (ether, −30 → 0 °C, 1 h, 70%) gave the *all-trans*-bromide **11**, which on treatment with



11, Y = CH_2Br



12, Y = CH_2–S⊕ Br⊖

tetrahydrothiophene yielded the salt **12** [MeOH–H_2O (9:1), room temperature, 1 h, 100%]. This material was used directly without

(1) Orange, R. P.; Austen, K. F. *Adv. Immunol.* **1969**, *10*, 105.
(2) Borgeat, P.; Hammarström, S.; Samuelsson, B., presented at the 1979 International Conference on Prostaglandins, Washington, D.C., May 1979. See: *Chem. Eng. News* **1979**, *57* (24), 19.
(3) Parker, C. W.; Huber, M. M.; Hoffman, M. K.; Falkenhein, S. F. *Prostaglandins* **1979**, *18*, 673.
(4) Hammerström, S.; Murphy, R. C.; Samuelsson, B.; Clark, D. A.; Mioskowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1266.
(5) Corey, E. J.; Yoshinobu, A.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748.
(6) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436.
(7) Brandsma, L. "Preparative Acetylenic Chemistry", Elsevier: Amsterdam, 1971.
(8) Available from Farchan, Division Chemsampco, Inc.; see also ref 7.
(9) Satisfactory ultraviolet, ^1H NMR, mass spectra, and elemental analyses were obtained for all intermediates.
(10) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

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