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ENANTIOSPECIFIC TOTAL SYNTHESIS OF (-)-MEGAPHONE BY A HIGHLY CONTROLLED CONSECUTIVE 1,4- AND 1,3-ASYMMETRIC INDUCTION[1)]

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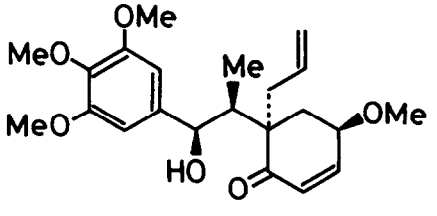
Summary: Enantiospecific total synthesis of (-)-megaphone (**1**) is reported. The key synthetic tactic is the use of (4S)-2Z-ethylidene-4-trityloxymethyl-butan-4-olide (**6**) to both establish the relative and absolute stereochemistry of the contiguous tertiary and quaternary carbon centers by a highly controlled 1,4- and 1,3-asymmetric induction and construct the 4-methoxy-6,6-dialkyl-cyclohexenone portion of **1**.

Control of the relative and absolute stereochemistry in the construction of the contiguous tertiary and quaternary carbon centers by the conjugate addition-enolate trapping, a double alkylation sequence using an activated olefin, has been recognized to have a high potential in biologically active natural products synthesis.[2,3)] Rare among these selective processes is the creation of new chiral carbon centers starting from an exo-cyclic olefin. We now report that lactones **7** and **8** bearing contiguous tertiary and quaternary carbon centers can be prepared from exo-alkylidene lactone **6** via highly controlled consecutive 1,4- and 1,3-asymmetric induction (Fig. 1).[4)] Furthermore, the method provides an efficient route to the enantiomerically pure cytotoxic neolignan (-)-megaphone **1**[5)] with the definite absolute configuration, which has been the focus of the current synthetic efforts.[6)] It is also noteworthy that optically pure lactone **5** both provides the chiral auxiliary for the asymmetric induction as well as the carbon framework of the target.



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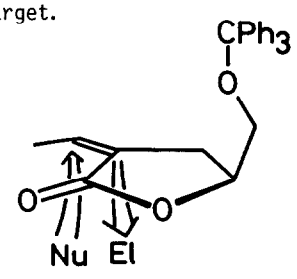

Fig. 1

Conjugate addition of lithiated 2-(3,4,5-trimethoxyphenyl)-1,3-dithiane to **6**,[7~9)] prepared from (S)-**5**,[10)] in THF at -78°C followed by alkylation with allyl bromide-HMPA at -78°C proceeded smoothly to afford crystalline **7** in 88% isolated yield.[11)] Two other minor isomers were detected by ^{1}H NMR of the crude products and the ratio was 23:1:1. Similarly lithiated tert-butyldimethylsilyldi(methylthio)methane reacted with high selectivity to afford, after protodesilylation with $(n\text{-Bu})_4NF$ in THF, **8** in 58% yield. The highly controlled

production of **7** and **8** via consecutive 1,4- and 1,3-asymmetric induction is attributable to effective shielding of the β-face of **6** by the trityloxymethyl group. Consequently, conjugate addition and alkylation occur from the α-face as shown in Fig. 1. As was shown by the X-ray crystallographic analysis, the bulky trityloxymethyl substituent was found to exist in a nearly axial-conformation with one of the phenyl rings situated just above the double bond of the exo-methylene portion (Fig. 2).[12] The favorable interaction (n_O-σ^*_{O-C}) of the etheral oxygen lone pair with the antibonding σ* of the O-C bond of the lactone ring may contribute strongly to the stabilization of this conformation.[13]

The contiguous tertiary and quaternary carbon centers of lactones **7** and **8** have the identical relative and absolute configuration with those of the proposed probable absolute structure of natural (-)-**1**.[5] First enantiospecific synthesis of (-)-**1** with definitive absolute configuration was carried out starting from **8**. In the following transformations, the lactone portion of **8** can be effectively utilized in constructing the requisite cyclohexenone framework of **1**.

Thus, simultaneous hydrolysis and alkoxide formation of **8** was carried out using a mixture of anhydrous KOH and KH in refluxing THF. Subsequent methylation with methyl iodide at -78°C to room temperature afforded the methyl ether **9** in 97% yield. Treatment of **9** with methyllithium in THF at -20°C afforded the methyl ketone **10** (82%). Detritylation with c. HCl in methanol (87%) and subsequent oxidation of the corresponding alcohol **11** with pyridine-SO_3, triethylamine in DMSO afforded the keto aldehyde **12** (67%). Next, base-catalyzed epimerization at the α-position of the aldehyde group with concomitant intramolecular aldol cyclization was effected by treating **12** with $NaHCO_3$ in refluxing methanol, producing a separable 4.6∿4.1:1 mixture of the expected cyclic enone **14** and its epimer in 59% yield.[14] Preferred formation of **14** can be rationalized based on the favorable conformation of the cyclization intermediate **13**, derived from the epimerized keto aldehyde, in which 1,3-diaxial interaction between allyl group and methoxy group is absent, while such severe interaction exists in the direct cyclization of **12**.

Enone **14** was then treated with mercuric chloride in aqueous acetonitrile to give the aldehyde **15** (91%). Finally, **15** was treated with 3,4,5-trimethoxyphenyllithium[15] in the presence of HMPA (4 eq) in THF at -78°C to afford crystalline (-)-megaphone **1** (46%, mp 151-2°C, mixed mp 150.5-2°C, $[\alpha]_D^{27}$-23°(EtOH); lit.,[5] mp 151.5-2.5°C, $[\alpha]_D^{27}$-23°(EtOH)) and (-)-isomegaphone **3** (28%). Oxidation of **1** with Jones reagent in acetone afforded (-)-oxidized megaphone **4**,[5] which was also obtained from **7**[11] with the definite absolute configuration via a similar route described above.[16] Synthetic **1**, **2**, and **4** were shown to be identical in all respects with natural **1** and **4** by direct comparison and with reported **2**[5].

This is the first asymmetric total synthesis of natural (-)-megaphone (**1**) by unambiguous construction of the absolute and relative stereochemistry of the four chiral centers via a highly controlled consecutive 1,4- and 1,3-asymmetric induction, and confirms that the absolute configuration previously ascribed to (-)-megaphone (**1**) is correct.

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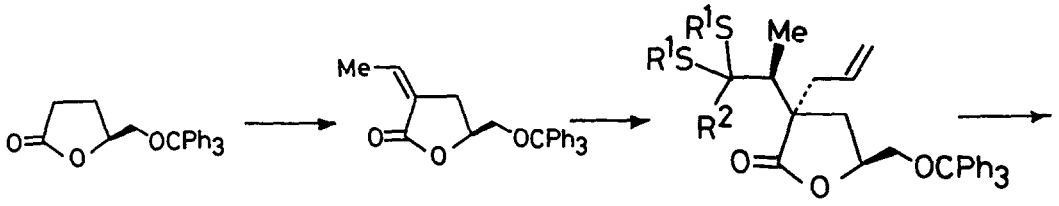
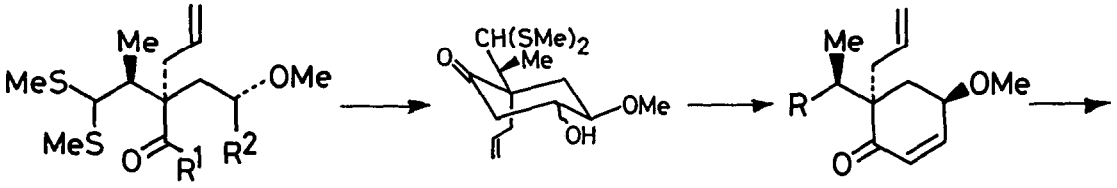


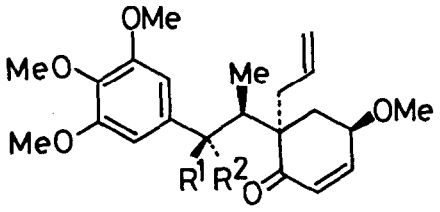
5 6 7 $R^1=(CH_2)_3$, $R^2=Ar$
8 $R^1=Me$, $R^2=H$



9 $R^1=OMe$, $R^2=CH_2OCPh_3$
10 $R^1=Me$, $R^2=CH_2OCPh_3$
11 $R^1=Me$, $R^2=CH_2OH$
12 $R^1=Me$, $R^2=CHO$

13

14 $R=CH(SMe)_2$
15 $R=CHO$



1 $R^1=OH$, $R^2=H$
2 $R^1=OAc$, $R^2=H$
3 $R^1=H$, $R^2=OH$
4 $R^1, R^2=O$

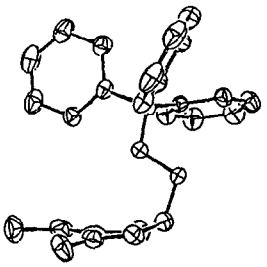


Fig. 2

References and Notes

1. This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
2. Review. K. Tomioka, K. Koga, "Asymmetric Synthesis," Ed. by J. D. Morrison: Academic Press, New York, 1983, Vol. 2, p. 201.
3. (a) K. Tomioka, F. Masumi, T. Yamashita, K. Koga, Tetrahedron Lett. **1984**, 25, 333; (b) T.

Takahashi, H. Okumoto, J. Tsuji, Tetrahedron Lett. **1984**, 25, 1925; (c) W. Oppolzer, R. Pitteloud, G. Bernardinelli, K. Baettig, Tetrahedron Lett. **1983**, 24, 4975; (d) G. H. Posner, J. P. Mallano, M. Hulce, L. L. Frye, J. Am. Chem. Soc. **1982**, 104, 4180; (e) T. Yanami, M. Miyashita, A. Yoshikoshi, J. Org. Chem. **1980**, 45, 607.

4. Approaches to the asymmetric synthesis of quaternary carbon centers have been reported. (a) Review: S. F. Martin, Tetrahedron, **1980**, 36, 419; (b) K. Tomioka, K. Ando, Y. Takemasa, K. Koga, J. Am. Chem. Soc. **1984**, 106, 2718; (c) A. I. Meyers, M. Harre, R. Garland, ibid. **1984**, 106, 1146; (d) G. Fráter, U. Müller, W. Günter, Tetrahedron, **1984**, 40, 1269; (e) S. Takano, C. Kasahara, K. Ogasawara, J. Chem. Soc. Chem. Commun. **1981**, 637, (f) K. Tomioka, Y.-S. Cho, F. Sato, K. Koga, Chemistry Lett. **1981**, 1621.
5. S. M. Kupchan, K. L. Stevens, E. A. Rohlfing, B. R. Sickles, A. T. Sneden, R. W. Miller, R. F. Bryan, J. Org. Chem. **1978**, 43, 586.
6. Syntheses of racemic **1** have been reported. (a) G. Büchi, P.-S. Chu, J. Am. Chem. Soc. **1981**, 103, 2719; (b) P. A. Zoretic, C. Bhakta, R. H. Khan, Tetrahedron Lett. **1983**, 24, 1125; (c) T. R. Hoye, M. J. Kurth, Tetrahedron Lett. **1983**, 24, 4769; (d) T. Matsumoto, S. Imai, S. Usui, A. Suetsugu, S. Kawatsu, T. Yamaguchi, Chemistry Lett. **1984**, 67; (e) Synthetic approach. J. P. Marino, J. C. Jaén, 4th ICOS ABSTRACTS (Tokyo), 1982, p.52.
7. Satisfactory spectroscopic and analytical data were obtained for all new compounds described in this communication.
8. Elimination reaction of the mesylate ($NaHCO_3$ in methanol at 50°C), obtained by the aldol reaction of the lithium enolate of **5** and CH_3CHO followed by mesylation, afforded a easily separable mixture of **6** (33%) and its E-isomer (36%). E-isomer was photochemically (acetone as a sensitizer in benzene, Hg lamp) isomerized to a nearly 1:1 mixture of **6** and E-isomer, affording **6** in 48% net yield from **5**.
9. Selected data. Optical rotations were measured in $CHCl_3$ at 25°C unless otherwise noted. **6**: mp110-112°C, $[\alpha]_D$+27.5°; **7**: mp198-199°C, $[\alpha]_D$-79.0°; **8**: mp129-131°C, $[\alpha]_D$+9.0°; **9**: $[\alpha]_D$-10.9°; **10**: $[\alpha]_D$-3.8°; **11**: $[\alpha]_D$+17.9°; **12**: $[\alpha]_D$-28.1°; **14**: $[\alpha]_D$+26.1°; **15**: $[\alpha]_D$ +58.6°; **3**: $[\alpha]_D$-21.3°(EtOH); **2**: $[\alpha]_D$-11.0°(EtOH); **4**: $[\alpha]_D$-60.0°.
10. K. Tomioka, H. Mizuguchi, K. Koga, Chem. Pharm. Bull. **1982**, 30, 4304.
11. The structure of **7** was unambiguously determined by X-ray analysis. Details will be reported in due course.
12. ^1H NMR analysis of **6** at 400 MHz also supported the predominant conformation as shown in Fig. 2. Details will be reported in due course.
13. See, for example, (a) I. Morishima, K. Yoshikawa, K. Bekki, J. Am. Chem. Soc. **1975**, 97, 4283; (b) G. R. Underwork, H. S. Friedman, ibid. **1974**, 96, 4689; (c) Review: P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," J. E. Baldwin, ed., Pergamon Press, Oxford, 1983.
14. Ratio of **14** to its epimer was dependent on the solvent, 2.8:1 in ethanol-water (1:1(v/v)) (68%), 2.3:1 in methanol-water (1:1(v/v)) (60%). Some attempts to isomerize at the center bearing methoxy group of the isomer failed to afford **14**.
15. I. Kozák, L. Kronrád, M. Procházka, J. Labelled Compd. Radiopharm. **1978**, 15 (Suppl. Vol.), 401.
16. Details will be published in due course.

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