ORGANIC LETTERS

2005
Vol. 7, No. 8
1581−1584

Synthesis of the Putative Structure of Tridachiahydropyrone

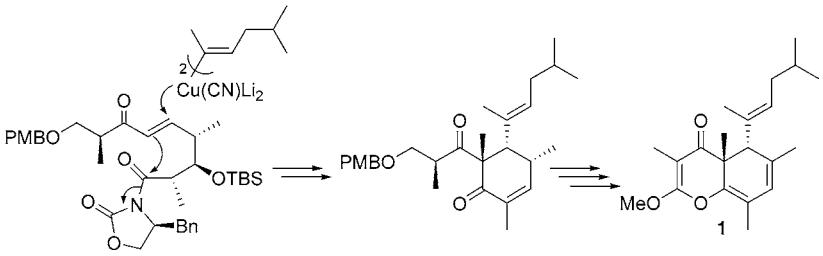
David W. Jeffery,[†] Michael V. Perkins,*[,†] and Jonathan M. White[‡]

School of Chemistry, Physics and Earth Sciences, Flinders University, G.P.O. Box 2100, Adelaide, S.A. 5001, Australia, and School of Chemistry, The University of Melbourne, Melbourne, Vic. 3010, Australia

mike.perkins@flinders.edu.au

Received February 4, 2005

ABSTRACT



A short total synthesis of the putative structure of the marine natural product tridachiahydropyrone as a single enantiomer is described. Novel steps include a cuprate addition and cyclization to form a cyclohexanone ring and formation of the bicyclic pyrone with P_2O_5 on Celite. The spectroscopic data obtained for compound 1 do not match those reported for tridachiahydropyrone; therefore, revision of the assigned natural product structure is warranted.

Tridachiahydropyrone was isolated in 1996 by Gavagnin et al.[1] from the sacoglossan mollusc, *Tridachia crispata*. The structure was assigned as compound **1** (Figure 1) by extensive NMR spectroscopic analysis, and the relative stereochemistry was assigned by NOE experiments; however, the absolute configuration was not determined. This compound is structurally interesting, possessing an unusual fused bicyclic pyrone. This ring system is accessible by our recently reported[2,3] methodology for the convergent total synthesis of enantiopure tridachione marine natural products. We now wish to describe the first, unambiguous total synthesis of compound **1** with the reported structure of tridachiahydropyrone, as a single enantiomer.

The retrosynthesis of compound **1** is analogous to that reported[3] for a model system, where pyrone **2** is proposed to be formed by cyclization of the enone oxygen onto the acid moiety of ketoacid **3**, followed by dehydration. Pyrone **2** could then be O-methylated to yield compound **1** (Scheme 1). Ketoacid **3** can be seen to come from the deprotection/oxidation of cyclohexenone **4**, which in turn arises from trans methylation and elimination of cyclohexenol **5**. Addition of cuprate **6** to enone **7**, using the tandem conjugate addition−cyclization procedure we have previously described,[2,3] produces enol **5**.

We began with enone **7**, obtained as previously described,[3] and synthesized cuprate precursor **8** (Scheme 2) on the basis

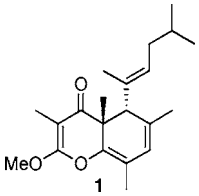


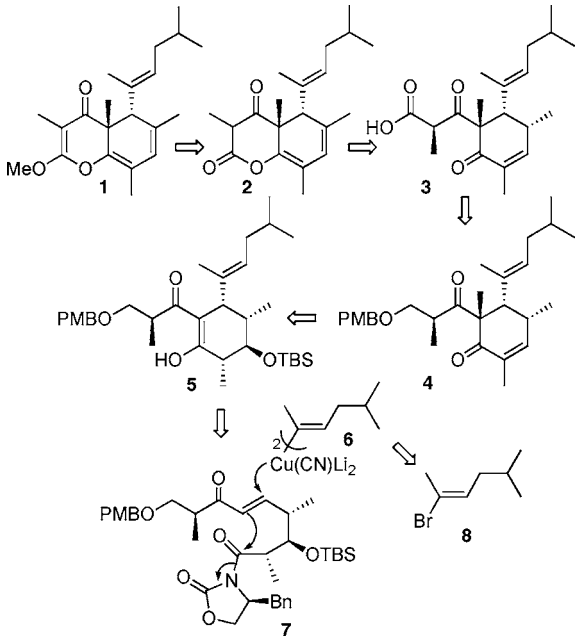
Figure 1. Structure reported[1] for tridachiahydropyrone.

[†] Flinders University.
[‡] The University of Melbourne.

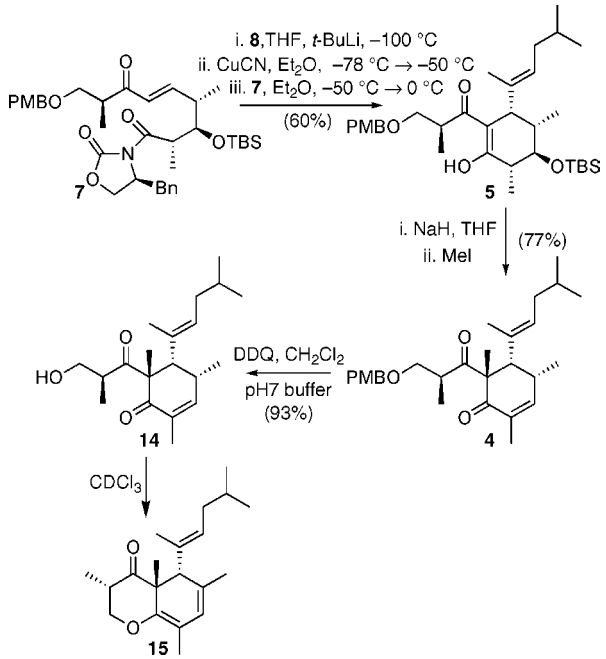
(1) Gavagnin, M.; Mollo, E.; Cimino, G.; Ortea, J. *Tetrahedron Lett.* **1996**, *37*, 4259−4262.
(2) Jeffery, D. W.; Perkins, M. V. *Tetrahedron Lett.* **2004**, *45*, 8667−8671.
(3) Jeffery, D. W.; Perkins, M. V.; White, J. M. *Org. Lett.* **2005**, *7*, 407−409.

10.1021/ol050236d CCC: $30.25
Published on Web 03/16/2005

Scheme 1

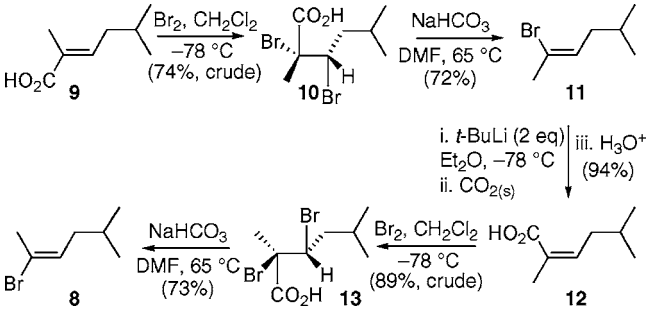


Scheme 3



of literature precedent.[4] The known[5] α,β-unsaturated acid **9** was stereospecifically brominated (Br_2, CH_2Cl_2, −78 °C)[4] to afford crystalline dibromide **10** (74%, crude), and the crude material was subjected to decarboxylative anti elimination conditions ($NaHCO_3$, DMF, 65 °C)[6] to yield volatile (*Z*)-vinyl bromide **11** (72%).

Scheme 2



Treatment of (*Z*)-bromide **11** with *t*-BuLi[7] in Et_2O at −78 °C (Scheme 2), followed by transferral of the organolithium solution into solid CO_2 and subsequent acidification, yielded the corresponding (*Z*)-α,β-unsaturated acid **12** (94%). An iteration of the above bromination procedure to give crystalline **13** (89%, crude), followed by decarboxylative elimination, yielded volatile (*E*)-vinyl bromide **8** (73%).[8] Purification of the liquid products was performed by distillation under reduced pressure. This somewhat circuitous route gave isomerically pure vinyl bromide **8** in reasonable yield (27%, six steps) and was amenable to scale-up.

With substantial quantities of cuprate precursor **8** in hand, we explored the conditions necessary for successful cuprate formation, subsequent 1,4 addition, and cyclization. Initially, problems were associated with the thermal instability of the derived organolithium solution. This obstacle was overcome by the use of a precooled cannula as described below. The use of various copper salts was also attempted, but CuCN (Aldrich) proved to be the most reliable. The final conditions we employed enabled the synthesis of **5** reproducibly, in 50−65% yield, exclusively as the enol tautomer (Scheme 3).

Treatment of a colorless solution of vinyl bromide **8** in THF with *t*-BuLi at −100 °C resulted in a bright yellow solution, with the color being indicative of the lithium−halogen exchange. This yellow organolithium solution was transferred quickly via a precooled cannula (−78 °C) into a $CuCN/Et_2O$ slurry at −78 °C, and the mixture was allowed to warm to −50 °C. The formation of a colorless, homogeneous solution after several minutes at −50 °C was diagnostic of successful preparation of cuprate **6**. Addition of enone **7** in Et_2O caused an immediate bright yellow coloration, and the reaction was stirred at −50 °C for 1 h (to ensure complete addition) and 0 °C for 1 h (to ensure complete cyclization) before being quenched (90% NH_4Cl/10%

(4) Kim, H.; Lee, S.-K.; Lee, D.; Cha, J. K. *Synth. Commun.* **1998**, *28*, 729−735.

(5) Villa, M.-J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1569−1572.

(6) Norris, W. P. *J. Org. Chem.* **1959**, *24*, 1579−1580.

(7) Care was needed with the amount of *t*-BuLi used; otherwise, the crude product was contaminated with pivalic acid. To overcome this, the *t*-BuLi was standardized prior to use by titration against *N*-pivaloyltoluidine (Suffert, J. *J. Org. Chem.* **1989**, *54*, 509−510.).

(8) All new compounds gave spectroscopic data in agreement with the assigned structures and copies of the NMR spectra, and spectral data for all new compounds are available in Supporting Information.

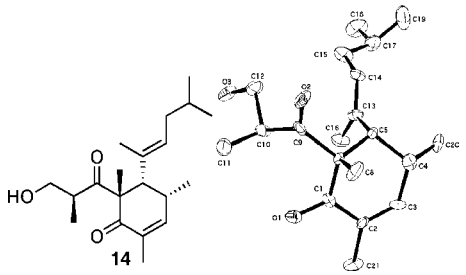


Figure 2. X-ray crystal structure of alcohol **14**.

NH_4OH), filtered through Celite, and purified by SiO_2 flash chromatography. The addition of the cuprate was highly selective for syn addition product **5**.

Subsequent trans (axial) methylation[2,3] (Scheme 3) proceeded with concurrent β-elimination of the OTBS group to afford cyclohexenone **4** (77%, stereochemistry confirmed by NOE experiments) with high selectivity for the trans product (>40:1 trans:cis, determined by ^{1}H NMR). Apparently, the extra steric bulk of the vinyl side-chain had a large directing influence when compared to the simple methyl group in the model (9:1 trans:cis).[3] Cyclohexenone **4** was deprotected[9] to give crystalline alcohol **14** (93%, Scheme 3). Compound **14** gave small, weakly diffracting crystals, but a crystal structure of sufficient quality to indicate the three-dimensional structure was obtained and showed the relative stereochemistry of the molecule as depicted in Figure 2.

This crystal structure highlights several important factors. The conjugate addition gave the Felkin−Anh-like product,[10] with induction coming from the γ-methyl in enone **7**. The side chain alkene has an (*E*)-configuration, and NaH/MeI methylation gave the product where the side chain and the methyl group are trans. Alcohol **14** was acid sensitive and cyclized readily in $CDCl_3$ to undesired pyrone **15** (Scheme 3). Alcohol **14** could be further manipulated provided that acidic conditions were avoided.

Dess−Martin oxidation[11] of alcohol **14** to crystalline aldehyde **16** (ca. 100%, crude, Scheme 4) proceeded with

Scheme 4

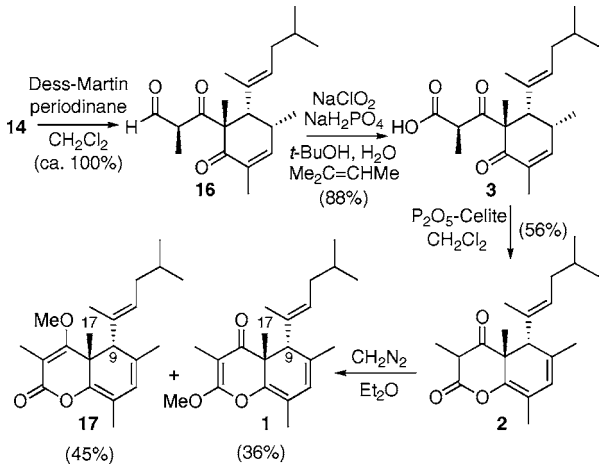
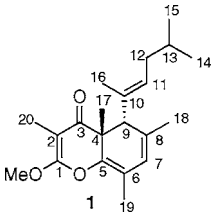


Table 1. Comparison of ^{1}H and ^{13}C NMR for Tridachiahydropyrone[1] and Synthetic **1** (Significant Differences in Bold)



carbon no.	tridachiahydropyrone[a] δ ^{1}H[c]	tridachiahydropyrone[a] δ ^{13}C[c]	synthetic **1**[b] δ ^{1}H[c]	synthetic **1**[b] δ ^{13}C[c]
1		165.97		164.17
2		87.88		88.94
3		195.79		192.83
4		46.56		46.17
5		145.33		145.80
6		115.74		112.14
7	5.44	121.28	5.48	121.45
8		134.42		133.59
9	**3.91**	**53.45**	**2.91**	**58.82**
10		133.42		132.54
11	5.51	130.37	5.39	128.05
12	1.90	37.24	1.80	36.90
13	1.64	28.72	1.63	28.94
14	0.88	22.59	0.82	22.24
15	0.88	22.47	0.82	22.30
16	1.53	13.71	1.47	13.38
17	**1.20**	**21.21**	**1.35**	**25.40**
18	1.63	21.72	1.75	21.67
19	1.75	14.62	1.75	14.31
20	1.63	7.40	1.60	6.46
OMe	3.96	55.08	3.94	54.69

[a] Bruker AMX 500 MHz NMR spectrometer. [b] Varian Gemini 300 MHz NMR spectrometer. Assignments assisted by ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMBC and HMQC (Inova 600 MHz NMR spectrometer). [c] Chemical shifts in ppm referenced to C*H*Cl$_3$ (δ 7.26) for proton resonances and to *C*DCl$_3$ (δ 77.0) for carbon resonances.

no detectable epimerization of the aldehyde α-stereocenter, as did $NaClO_2$ oxidation,[12] with modified product isolation,[13] affording ketoacid **3** (88%). Treatment of acid **3** in CH_2Cl_2 with Eaton's reagent (P_2O_5−$MeSO_3H$),[14] as previously described,[3] yielded a mixture of products, none of which involved the desired cyclization. This was apparent from the presence of the enone vinyl proton singlet at ca. 6.3 ppm and the loss of the side-chain vinyl proton triplet at ca. 5.1 ppm in the ^{1}H NMR spectrum of the crude product. Clearly, the acidic conditions were not compatible with the presence of the side-chain alkene.

A modification involved supporting P_2O_5 on oven-dried Celite,[15] followed by the addition of acid **3** in CH_2Cl_2 and stirring at room temperature (Scheme 4). This method

(9) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544.
(10) Chounan, Y.; Ono, Y.; Nishii, S.; Kitahara, H.; Ito, S.; Yamamoto, Y. *Tetrahedron* **2000**, *56*, 2821−2831.
(11) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(12) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron Lett.* **1980**, *37*, 2091−2096.

afforded pyrone **2** (56%), predominantly as the keto tautomer, after filtration and purification. Treatment of pyrone **2** with CH_2N_2 in Et_2O gave a 1.3:1 mixture of readily separable α-pyrone **17** (45%) and γ-pyrone **1** (36%). The structures of **17** and **1** were confirmed by extensive NMR studies, and strong NOEs were observed between H-9 and H-17 in both **17** and **1**, confirming the trans relationship of the side chain and methyl group.

The reported spectra of tridachiahydropyrone[1] were compared with those of synthetic **1**. The ^{13}C NMR spectra were significantly different, with a large disparity in the chemical shifts of C-9 and C-17. There was also a 1.0 ppm difference between the chemical shift of H-9 in the ^1H NMR spectra of the synthetic material and the natural product (Table 1). Visual comparison of copies of ^1H and ^{13}C NMR spectra of the natural product[16] and the synthetic material **1** confirmed these differences.

While the EI mass spectra were virtually identical, the UV/vis absorbances (in MeOH) were slightly different (**1** λ_{max} 262 nm, (ϵ 9020); tridachiahydropyrone λ_{max} 271 nm, (ϵ 10 840)), as were the optical rotations (**1** $[\alpha]_D$ −542 (*c* 0.26, $CHCl_3$); tridachiahydropyrone $[\alpha]_D$ −476 (*c* 0.49, $CHCl_3$)). Finally, while tridachiahydropyrone was reported to be crystalline, pyrone **1** failed to solidify and also decomposed in $CDCl_3$ (or $CHCl_3$) over time, partly reverting to the parent pyrone **2**. We therefore conclude that the previously assigned structure of tridachiahydropyrone is not correct and warrants revision. It appears that tridachiahydropyrone is a diastereomer of compound **1**.

In summary, we have applied our methodology for the synthesis of tridachione marine natural products to the formation of compound **1** with the reported structure of tridachiahydropyrone as a single enantiomer. We utilized a conjugate addition−cyclization approach, with the novel, bicyclic pyrone formation being accomplished under P_2O_5-mediated cyclization conditions. We are exploring alternative possibilities in an attempt to determine the true structure of tridachiahydropyrone.

Acknowledgment. We wish to thank the Australian Research Council for funding and Flinders University for its support and facilities. We are also grateful to Dr. M. Gavagnin for the copies of tridachiahydropyrone spectra and for useful discussions.

Supporting Information Available: Copies of NMR spectra for all new compounds (and tridachiahydropyrone), data for all new compounds (including CIF for **14**), and experimental procedures for compounds **1**−**5** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050236D

(13) Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000**, *65*, 7456−7467.

(14) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071−4073.

(15) Puglisi, C. J.; Elsey, G. M.; Prager, R. H.; Skouroumounis, G. K.; Sefton, M. A. *Tetrahedron Lett.* **2001**, *42*, 6937−6939.

(16) Copies of the original ^1H and ^{13}C NMR spectra of tridachiahydropyrone were obtained for comparison.