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A Synthesis of the Ring System of Terpestacin

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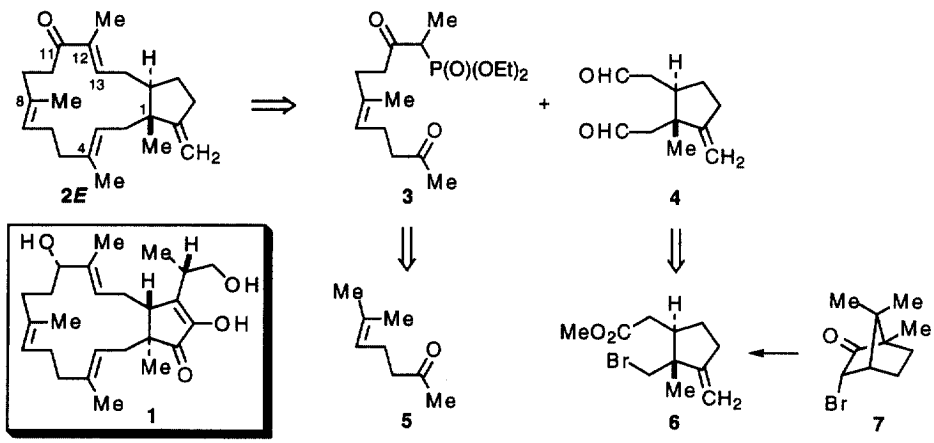
Abstract: The ring system of the sesterterpene terpestacin has been obtained from a cyclopentanic precursor prepared from *endo*-3-bromocamphor and from an acyclic keto phosphonate prepared from 6-methylhept-5-en-2-one. The connection of both compounds has been achieved by a Horner-Wadsworth-Emmons reaction on the one hand and by a McMurry reaction on the other.

Keywords: terpenes; macrocycles; Wittig reactions; McMurry reactions.

The sesterterpene terpestacin **1** was isolated in the early nineties from the fermentation metabolites of a fungal *Arthrinium* sp. strain and was shown to be a HIV syncytia formation inhibitor.[1] It exhibits a new bicyclic framework which was synthesised earlier by the group of Yoshii.[2] The recent publication of a total synthesis of racemic terpestacin by Tatsuta *et al.*[3] prompts us to report our own approach to terpestacin.[4]



Scheme 1.

The retrosynthetic disconnection outlined in Scheme 1 led us to consider a synthesis from an acyclic synthon **3** on the one hand and from a cyclopentanoid dialdehyde synthon **4** on the other. It seemed clear that we could rely on a Horner-Wadsworth-Emmons (HWE) reaction for the northern connection, whereas a McMurry reaction seemed a reasonable choice for the southern.[5] We planned to obtain the acyclic precursor from 6-methylhept-5-en-2-one **5** and the cyclopentanoid moiety from the bromo ester **6** which can be prepared according to Money from

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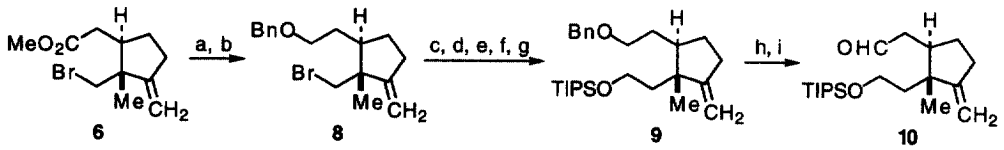
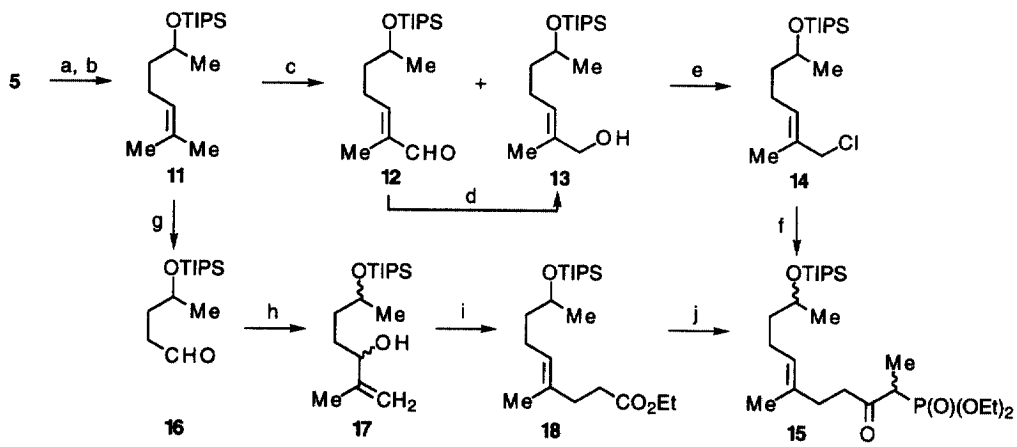
endo-3-bromocamphor **7**.[6] Both enantiomers of this compound are commercially available, but, since the *endo*-(–)-3-bromocamphor needed to obtain natural (+)-terpestacin is about twenty times more expensive than its (+)-enantiomer, we decided to run our model studies starting from the latter. In this letter, we report the synthesis of the ketone **2*E*** displaying the bicyclic system of terpestacin.



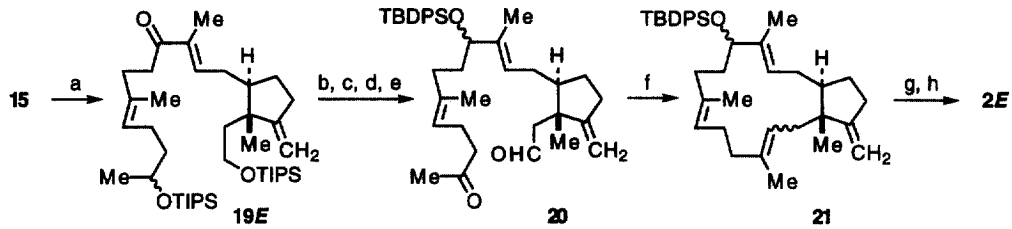
Scheme 2. a) $LiAlH_4$, Et_2O, –60 °C, 1.5 h (94%); b) $KN(TMS)_2$, THF, 0 °C, 0.5 h, then BnBr (93%); c) NaCN, DME:HMPA 3:2, 100 °C, 2 days (93%) ; d) DIBAH, toluene, 0 °C, 0.5 h; e) H_3O^+ (steps d + e: 70%); f) $LiAlH_4$, Et_2O, 0 °C, 0.5 h (92%); g) TIPSCl, imidazole, DMF, 12 h (97%); h) Li, $EtNH_2$, THF, –78 °C, 1.5 h (97%); i) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C, 4 h, then NEt_3 (98%).

The starting bromo ester **6** had first to undergo a homologation on its southern appendage (Scheme 2). Reduction of the carboxymethyl and benzylation of the resulting hydroxyl gave the bromo ether **8** which was substituted with sodium cyanide, reduced to an aldehyde and then to an alcohol, which was protected as its triisopropylsilyl (TIPS)[7] ether **9**. Conversion of **9** to aldehyde **10**[8] was achieved by removal of the benzyl group and Swern oxidation.[9] It is worth mentioning at this point that we have chosen to transform the oxygen containing functional groups to the corresponding alcohols since a bigger choice of protecting groups is available for alcohols compared to aldehydes or ketones. We have selected the TIPS protecting group because, unlike the *tert*-butyldiphenylsilyl (TBDPS) group, it is not affected by the dissolving metal conditions used in the debenzylation reaction. In addition, we already foresaw that prior to the McMurry reaction we might have to protect the C-11 oxygen containing function by a group which would survive the TIPS deprotection.



Scheme 3. a) $LiAlH_4$, Et_2O, 0 °C, 1 h (100%); b) TIPSCl, imidazole, DMF, r. t., 8 h (100%); c) SeO_2, *t*-BuO_2H, salicylic acid, CH_2Cl_2, r. t., 2.5 days; d) $NaBH_4$, EtOH, 0 °C, 0.5 h (steps c + d: 61% of **13**); e) MsCl, LiCl, collidine, DMF, 0 °C, 2 h (96%); f) $LiCH_2C(O)C(Me)NaP(O)(OEt)_2$, THF, 0 °C (56%); g) O_3, CH_2Cl_2, then Me_2S, 12 h (100%) h) CH_2=C(Me)MgBr, THF, r. t., 0.5 h (94%); i) $MeC(OEt)_3$, $EtCO_2H$ (0.06 equiv.), 140 °C, 1.5 h (89%); j) $MeCHLiP(O)(OEt)_2$, THF, –78 °C, 15 min. (94%).

The synthesis of the acyclic intermediates **15** (Scheme 3) was initiated by reduction of the methylheptenone **5**, and TIPS protection of the resulting alcohol to give ether **11**. Two routes to **15** were then explored. The first involved the allylic oxidation of **11** with selenium dioxide[10] followed by the transformation of the resulting alcohol **13** into the chloride **14**[11] and its treatment with the dianion deriving from diethyl (1-methyl-2-oxopropyl)phosphonate.[12] However, the yield of keto phosphonates **15** was variable and generally modest. In the alternative route, ozonolysis of **11** produced **16**, which was transformed to alcohol **17** by addition of isopropenylmagnesium bromide and, subsequently, to γ,δ-unsaturated ester **18**[13] by subjection to the Johnson variant of the Claisen rearrangement.[14] Eventually, reaction with the lithio derivative of triethyl phosphonate allowed the obtention of the keto phosphonates **15**[8] in 78% yield from **11**.



Scheme 4. a) $KN(TMS)_2$, dibenzo-18-crown-6, toluene, r. t., 2 h, then **10**, 0.5 h (84%; **19*E*/19*Z*** = 86/14); b) DIBAH, toluene, 0 °C (88%); c) TBDPSCl, imidazole, DMF, r. t., 1 day (95%); d) *n*-Bu_4NF, THF, 25 °C, 15 h (86%); e) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C, 2 h, then NEt_3 (80%); f) $TiCl_3$, Zn-Cu, DME, 80 °C, then addition of **20** *via* syringe pump over 24 h (54%); g) *n*-Bu_4NF, THF, reflux, 24 h (100%); h) *n*-Pr_4NRuO_4, NMO, 4 Å molecular sieves, CH_2Cl_2, r. t., 2 h (94%; **2*E*/2*Z*** = 64/36).

With compounds **10** and **15** at hand, we could start building the 15-membered macrocycle (Scheme 4). A HWE reaction gave a mixture of enones **19*E*** and **19*Z*** in 84% yield (***E*** / ***Z*** = 86/14).[15] After separation by column chromatography, the ***E*** isomer was transformed into a mixture of two allylic TBDPS ethers[16] which, by selective removal of the TIPS groups and Swern oxidation, furnished the keto aldehydes **20**[17] needed for the McMurry reaction. This reaction was first attempted with low-valent titanium prepared according to Clive ($TiCl_3/C_8K$, 1/2 molar ratio)[18] but, in our hands, it resulted only in a 10-15% yield of macrocyclic products. Since almost no other material could be recovered, we suspected that the problem lay in the desorption of the products from the graphite. We then turned to the classical McMurry conditions ($TiCl_3$-Zn/Cu couple)[19] which allowed us to obtain a mixture of four diastereomeric macrocyclic ethers **21** in an unoptimised 54% yield. The ***E*** / ***Z*** ratio of the newly formed double bond was shown to be 64/36 after removal of the TBDPS protecting group and reoxidation of the alcohols[20] to a mixture of ketones **2*E*** and **2*Z***[17,21] which were separated by careful column chromatography.

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References and Notes

1. Iimura, S.; Oka, M.; Narita, Y.; Konishi, M.; Kakisawa, H.; Gao, Q.; Oki, T. *Tetrahedron Lett.* **1993**, *34*, 493-496. Oka, M.; Iimura, S.; Narita, Y.; Furumai, T.; Konishi, M.; Oki, T.; Gao, Q.; Kakisawa, H. *J. Org. Chem.* **1993**, *58*, 1875-1881.
2. Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1995**, 249-250.

3. Tatsuta, K.; Masuda, N.; Nishida, H. *Tetrahedron Lett.* **1998**, *39*, 83-86.
4. Presented in part at the GECO XXXVIII meeting, Mittelwihr (France), 24-29 August 1997.
5. Examples of McMurry macrocyclisations are reviewed in: McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-1524; Fürstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442-2469; Lectka, T. The McMurry reaction. In: Fürstner, A., editor. Active Metals. Weinheim, VCH, **1996**, 85-131. A macrocycle bearing an allylic silyl ether is obtained in: Li, Y.; Li, W.; Li, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2953-2956.
6. Hutchinson, J. H.; Money, T.; Piper, S. E. *Can. J. Chem.* **1986**, *64*, 854-860. See also: Clase, J. A.; Money, T. *Can. J. Chem.* **1992**, *70*, 1537-1544. In our experience, the reduction of 3,9,10-tribromocamphor into 9,10-dibromocamphor with zinc-acetic acid was best performed at 18 °C.
7. Rücker, C. *Chem. Rev.* **1995**, *95*, 1009-1064.
8. ^{1}H NMR (200 MHz, $CDCl_3$). *Aldehyde **10***: δ 0.89 (s, 3 H); 1.04 (br s, 21 H); 1.27 (m, 1 H); 1.73 (t, *J* = 7.1 Hz, 1 H); 1.74 (t, *J* = 6.8 Hz, 1 H); 1.83-1.99 (m, 1 H); 2.21 (ddd, *J* = 15.4, 10.2, 2.8 Hz, 1 H); 2.22-2.52 (m, 3 H); 2.57 (ddd, *J* = 15.4, 3.3, 1.4 Hz, 1 H); 3.70 (t, *J* = 6.9 Hz, 2 H); 4.74 (br t, *J* = 2.3 Hz, 1 H); 4.91 (br t, *J* = 2.0 Hz, 1 H); 9.78 (dd, *J* = 2.8, 1.4 Hz, 1 H). *Keto phosphonates **15***: δ 1.05 (br s, 21 H); 1.15 (d, *J* = 6.0 Hz, 3 H); 1.32 and 1.33 (2 t, *J* = 7.1 Hz, 6 H); 1.34 (dd, *J* = 17.5, 7.1 Hz, 3 H); 1.60 (br s, 3 H); 2.00 (br q, *J* = 7.6 Hz, 2 H); 2.25 (br t, *J* = 7.5 Hz, 2 H); 2.64 (dt, *J* = 17.2, 7.6 Hz, 1 H); 2.87 (dt, *J* = 17.2, 7.8 Hz, 1 H); 3.22 (dq, *J* = 25.0, 7.1 Hz, 1 H); 3.91 (sext., *J* = 5.8 Hz, 1 H); 4.12 (several q, *J* = 7.1 Hz, 4 H); 5.13 (br t, *J* = 6.4 Hz, 1 H).
9. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.
10. Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528.
11. Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044-3045.
12. Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071-3072.
13. The ester **18** consisted of more than 95% *E* isomer (gas chromatography) and was used as it was.
14. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741-743.
15. Determined by 200 MHz ^{1}H NMR on the H-13 signal which was at δ 5.67 for **19*Z*** and δ 6.65 for **19*E***.
16. The stereoselective reduction of the carbonyl group will be addressed later.
17. ^{1}H NMR (500 MHz, $CDCl_3$). *Keto aldehydes **20***: δ 0.96 and 0.97 (2 s, 3 H); 1.04 and 1.05 (2 s, 9 H); 1.21-1.30 (m, 1 H); 1.44 and 1.45 (2 br s, 3 H); 1.51-1.61 (m, 2 H); 1.57 (br s, 3 H); 1.62-1.78 (m, 5 H); 1.94-2.03 (m, 1 H); 2.11 (s, 3 H); 2.18 (br q, *J* = 7.4 Hz, 2 H); 2.23-2.34 (m, 1 H); 2.38 (t, *J* = 7.4 Hz, 2 H); 2.40-2.45 (2 dd, *J* = 15.6, 3.4 Hz, 1 H); 2.41-2.49 (m, 1 H); 2.46-2.51 (2 dd, *J* = 15.6, 2.4 Hz, 1 H); 3.96 and 3.97 (2 t, *J* = 7.4 and 7.0 Hz, 1 H); 4.83 and 4.84 (2 t, *J* = 2.2 Hz, 1 H); 4.90 (br t, *J* = 7.2 Hz, 1 H); 4.97 and 4.98 (2 t, *J* = 2.7 Hz, 1 H); 5.00 and 5.02 (2 t, *J* = 7.0 and 6.5 Hz, 1 H); 7.30-7.44 (m, 6 H); 7.60 (m, 2 H); 7.66 (m, 2 H); 9.67 and 9.68 (2 dd, *J* = 3.4, 2.4 Hz, 1 H). *Ketone **2Z*** δ 0.92 (s, 3 H); 1.61 (s, 6 H); 1.81 (s, 3 H); 2.07-2.50 (m, 13 H); 3.00 (m, 1 H); 4.65 (t, *J* = 2.2 Hz, 1 H); 4.78 (br t, *J* = 6.0 Hz, 1 H); 4.88 (t, *J* = 2.0 Hz, 1 H); 5.05 (br t, *J* = 5.4 Hz, 1 H); 6.72 (br t, *J* = 7.4 Hz, 1 H). *Ketone **2E*** δ 0.92 (s, 3 H); 1.54 (s, 3 H); 1.58 (s, 3 H); 1.73 (s, 3 H); 2.58 (ddd, *J* = 13.0, 7.0, 6.0 Hz, 1 H); 2.73 (dt, *J* = 13.0, 7.8 Hz, 1 H); 4.78 (t, *J* = 2.3 Hz, 1 H); 4.91 (t, *J* = 2.0 Hz, 1 H); 5.02 (br t, *J* = 5.6 Hz, 1 H); 5.06 (m, 1 H); 6.59 (br t, *J* = 7.5 Hz, 1 H).
18. Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018-3028.
19. McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655-2656. McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255-3266. Use of the $TiCl_3(DME)_{1.5}$ complex instead of $TiCl_3$ did not allow us to improve our yield.
20. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627.
21. The assignment of the *E* and *Z* configurations is based on the ^{13}C NMR signals of the methyls (from a ^{1}H,^{13}C-HMQC experiment; $CDCl_3$): ***2Z*** δ 11.7 (Me-12), 17.4 (Me-8), 22.1 (Me-4), 24.6 (Me-1); ***2E*** δ 11.0 (Me-12), 15.2 and 15.7 (Me-8, Me-4), 23.4 (Me-1). The *E* / *Z* ratio has been determined by 200 MHz ^{1}H NMR.