Tetrahedron Letters, Vol.22, No.42, pp 4193 - 4196, 1981
Printed in Great Britain

0040-4039/81/424193-04$02.00/0

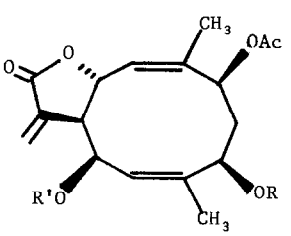
SYNTHESIS OF 4-SUBSTITUTED CIS,CIS-1,6-CYCLODECADIENES VIA CYCLOALKYLATION

Mark S. Frazza and Bryan W. Roberts*
Department of Chemistry
University of Pennsylvania
Philadelphia, Pa. 19104, U.S.A.

Abstract: Cycloalkylation of dimethyl malonate and tosylmethylisocyanide with cis,cis-1,9-dibromonona-2,7-diene has demonstrated the feasibility of direct cyclization as a route to functionalized cis,cis-1,6-cyclodecadienes.

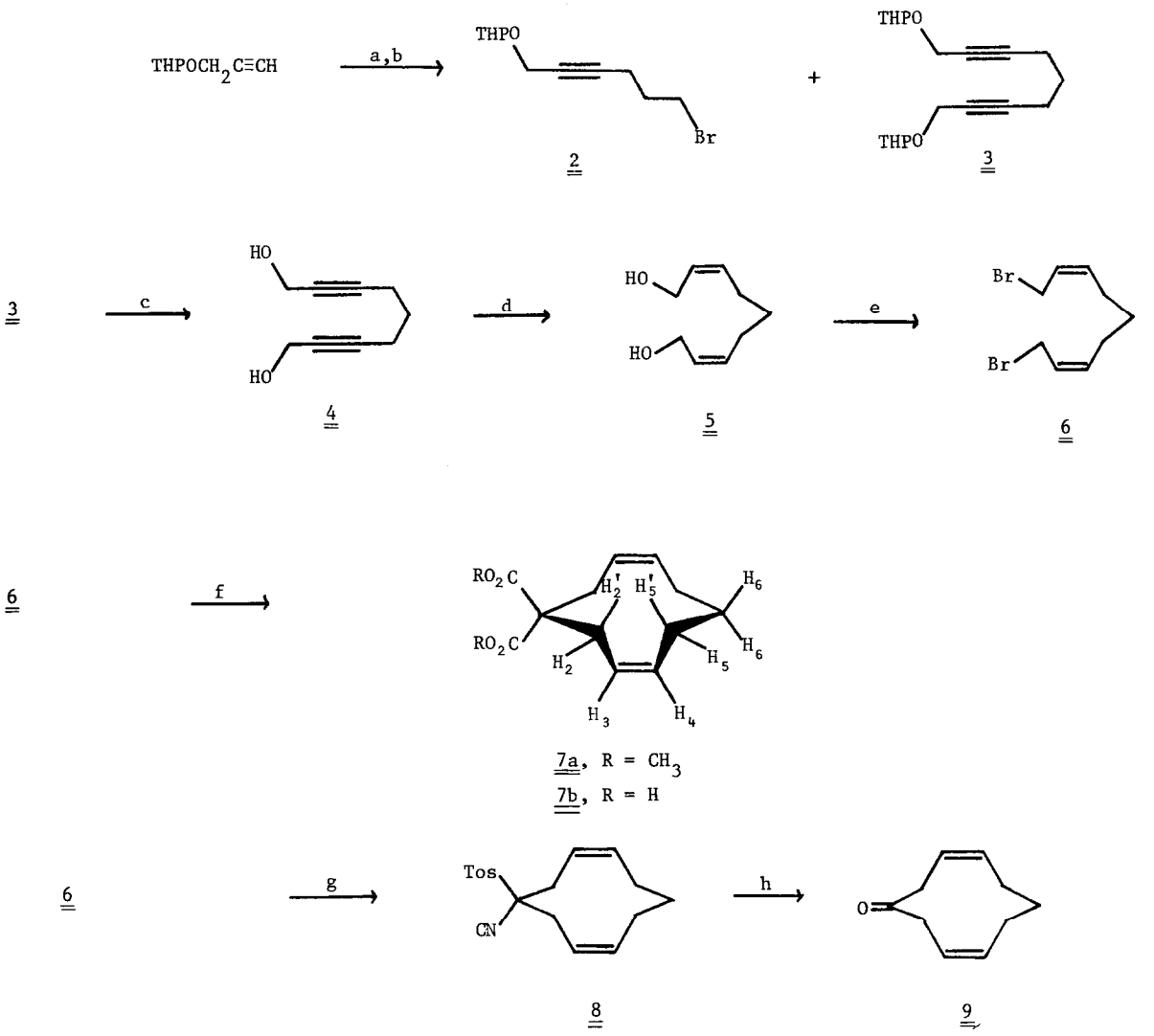
Eupacunin(1a), an antileukemic sesquiterpene lactone isolated from Eupatorium cuneifolium, is one of a small number of germacranolides reported to contain the cis,cis-1,6-cyclodecadiene ring system.[1] This feature, together with the existence of the o-bromobenzoate 1b in the less favored boat conformation[2] in the crystal[1a] led us to consider approaches to the total synthesis of this natural product. Construction of the medium ring diene by a method compatible with controlled incorporation of a number of substituents, especially allylic oxygen functionality, is essential to development of a rational strategy, and we have consequently turned our initial efforts toward this aspect of the problem. Known approaches to cis,cis-1,6-cyclodecadienes[3] did not appear sufficiently flexible for this purpose. However, the efficient formation of 4,9-dihetero analogues via double cycloalkylation with 1,4-dihalo-cis-2-butenes,[2a,4] together with the unique conformational properties of the ring system,[2] suggested that cycloalkylation with a bis(allylic) substrate such as 6, in which S_N2' processes are not likely to intervene,[3b] should be feasible and serve as a useful model for testing a direct cyclization approach to the diene system. Experiment has now confirmed this prediction, and we report here the preparation of dibromide 6 and its successful conversion to cis,cis-cyclodeca-3,8-dien-1-one (10).

Reaction of 2.1 equiv. of $THPOCH_2C{\equiv}CLi$ ($THPOCH_2C{\equiv}CH$, n-BuLi, THF), with 1,3-dibromopropane (THF, 72h reflux) followed by MPLC separation on silica (20% EtOAc-hexanes)[5] afforded 2 (R_f=0.36)[6] and 3 (R_f=0.27)[7] in 31% and 41% yields, respectively.[8] Additional 3 was obtained by further reaction of 2 with 1.5 equiv. of $THPOCH_2C{\equiv}CLi$ (THF, 48h reflux, 63%). Methanolysis of 3 (p-TsOH, CH_3OH, 3-5h reflux) gave 4, m.p. 40-41°, in 75-80% yield after flash column chromatography (Et_2O, R_f=0.34)[9] and recrystallization from ether/pet. ether. Two successive refluxings[10] and separations were necessary for an acceptable yield since complete conversion



1a, R = H; R' = angeloyl

1b, R = o-bromobenzoyl; R' = angeloyl



a) n-BuLi/THF; b) $Br(CH_2)_3Br$/THF/reflux/3d; c) p-TsOH/MeOH/reflux; d) Lindlar cat./H_2(2atm.)EtOAc; e) $CBr_4/Ph_3P/CH_2Cl_2/0^o$; f) $CH_2(CO_2Me)_2$/KH/THF; g) TosMIC/KH/THF; h) 40% HCl/Et_2O/CH_2Cl_2.

would not occur in one step, even under extended refluxing and a variety of cleavage conditions. The bis(acetylenic) diol was reduced to bis(allylic) diol 5 [Lindlar catalyst, H_2(2atm.), EtOAc], which was converted without further purification to the dibromide 6[11] (Ph_3P, CBr_4, CH_2Cl_2, 0^o, 65-73% from 4).[12] This thermally unstable compound was reacted further immediately after distillation (b.p. 65-70°/0.05mm).

Dropwise addition of a small excess of 6 to a solution of dimethyl malonate in THF containing 3 equiv. of KH and subsequent stirring for 13h at ambient temperature produced cyclodecadiene 7a[13,14] in 38% yield. The yield of 7a was significantly improved by use of high dilution

conditions. Addition of a solution of dimethyl malonate and dibromide 6 in THF to a THF suspension of 3 equiv. of KH over a period of 7.5h at ambient temperature and further stirring for 6h afforded 61% of 7a. With malonate 6 in hand, attempts were made to convert it to dienone 9.

Saponification of 7a (KOH, EtOH, H_2O, reflux 10h) afforded diacid 7b (white needles, m.p. 209.5-210.5°) after purification by TLC (C_6H_6-CH_3OH-HOAc, 45:8:4, R_f=0.40) and recrystallizatio from ethanol. However, all attempts to convert 7b to 9 using lead tetraacetate[15] or a double Curtius rearrangement[16] were unsuccessful, and the use of a more suitable formaldehyde dianion equivalent for reaction with 6 was consequently investigated. Methyl methylthiosulfoxide was examined initially due to its previously reported use in producing cyclic ketones from α,ω-dihalides,[17] but repeated attempts at cyclization gave only difficultly separable mixtures which failed to produce dienone 9 upon hydrolysis.

Subsequent evaluation of a number of other formaldehyde dianion equivalents prompted us to investigate the use of tosylmethylisocyanide (TosMIC).[18] Reaction of 6 with TosMIC under the high dilution conditions described above afforded 8 (m.p. 94-95° dec.) in 59% yield after purification by MPLC (15% acetone-hexanes, R_f=0.28) and recrystallization from aqueous ethanol. Acid catalyzed hydrolysis[18a] of 8 (40% aqueous HCl, 3:1 Et_2O-CH_2Cl_2) followed by extractive workup and sublimation of the crude product afforded 9 (m.p. 90.5-91.5°) in 54% yield.[19]

These results demonstrate that functionalized cis,cis-1,6-cyclodecadienes may be synthesized in preparatively useful yields by double displacement ring closure with the proper choice of nucleophile. Extension of this chemistry to more structurally complex systems is currently under investigation as a route to germacranolides.

Acknowledgement: The Bruker 250-MHz spectrometer used in this work was purchased with funds provided in part by a grant from the Chemical Instrumentation program of the National Science Foundation.

References and Notes

1. (a) S.M. Kupchan, M. Maruyama, R.J. Hemingway, J.C. Hemingway, S. Shibuya, T. Fujita, P.D. Cradwick, A.D.U. Hardy, and G.A. Sim, J. Am. Chem. Soc., 93, 4914(1971): (b) S.M. Kupchan, M. Maruyama, R.J. Hemingway, J.C. Hemingway, S. Shibuya, and T. Fujita, J. Org. Chem., 38, 2189(1973): (c) W. Herz, R. de Groote, R. Murari, and J.F. Blount, J. Org. Chem., 43, 3559(1978): (d) W. Herz, S.V. Govindan, and J.F. Blount, J. Org. Chem., 46, 761(1981).

2. (a) A. Feigenbaum and J.-M. Lehn, Bull. Soc. Chim. Fr., 198(1973); (b) B.W. Roberts, J.J. Vollmer, and K.L. Servis, J Am. Chem. Soc., 96, 4578(1974).

3. (a) D.J. Cram and N.L. Allinger, J. Am. Chem. Soc., 78, 2518(1956); (b) K.C. Murdock and R.B. Angier, J. Org. Chem., 27, 2395(1962); (c) R.M. Gipson, H.W. Guin, S.H. Simonsen, C.G. Skinner, and W. Shive, J. Am. Chem. Soc., 88, 5366(1966); (d) C.A. Grob, and P.W. Schiess, Helv. Chim. Acta, 43, 1546(1960); (e) A. Shani, Isr. J. Chem., 13 35(1975); (f) P. Heimbach, Angew. Chem. Intern. Ed. Engl., 5, 595(1966); (g) A. Horinaka, R. Nakashima, M. Yoshikawa, and T. Matsuura, Bull. Chem. Soc. Jpn., 48, 2095(1975); (h) S.W. Taylor and C.B. Rose, J. Org. Chem., 42 2175(1977); (i) F.E. Ziegler and J.J. Piwinski, J. Am. Chem. Soc., 101, 1611(1979).

4. W. Reppe, et al., Ann., 596, 80(1955) (see p. 132).

5. A medium pressure liquid chromatography apparatus constructed according to Meyers, et al. [A.I. Meyers, J. Slade, R.K. Smith, E.D. Mihelich, F.M. Hershenson, and C.D. Liang, J. Org. Chem., 44, 2247(1979)] was utilized.

6. S. Danishefsky, R. McKee, and R.K. Singh, J. Am. Chem. Soc., 99, 4783(1977).

7. Infrared spectra, low resolution mass spectra, 250 MHz proton nmr spectra, and combustion analyses (except as noted for compounds 5 and 6) were in accord with assigned structures of all compounds reported herein.

8. This is an optimized yield of 3. Apparently dialkylation is less favored with the 1,3-dibromide and requires extensive refluxing. Cf., P.J.M. Reijnders, H.R. Fransen, and H.M. Buck, Recl. Trav. Chim. Pays-Bas, 98, 511(1979).

9. W.C. Still, M. Kahan, and A. Mitra, J. Org. Chem., 43, 2923(1978)

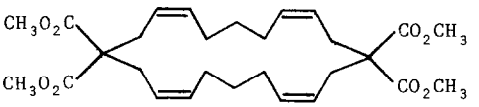
10. Cf., A.I. Rachlin, N. Wasyliw, and M.W. Goldberg, J. Org. Chem., 26, 2688(1961).

11. IR($CHCl_3$): 1650(w), 1450(m), 1200(s), and 700(m) cm^{-1}; ^1H NMR($CDCl_3$, 250MHz): δ1.55(2H, quintet, J = 7.3Hz, $-CH_2\underline{CH_2}CH_2-$), 2.18(4H, q, J = 7.3Hz, $=CHCH_2\underline{CH_2}-$), 4.00(4H, d, J = 8.3Hz, $-\underline{CH_2}Br$), and 5.69(4H, m, $-\underline{CH}=\underline{CH}-$); m/e 280, 282, 284.

12. P.J.Kocienski, G. Cernigliaro, and G. Feldstein, J. Org. Chem., 42, 353(1977).

13. IR($CHCl_3$): 1725(s), 1450(m), and 710(m) cm^{-1}; ^1H NMR($CDCl_3$, 250MHz): δ1.54(2H, m, H_6), 1.85 and 2.18-2.35(2H each, m's, H_5, H_5'), 2.40 and 2.80(2H each, m's, H_2, H_2'), 3.76(6H, s, $-OCH_3$), 5.11(2H, m, H_3), and 5.41(2H, m, H_4): ^{13}C NMR($CDCl_3$, 62.9MHz): δ24.50(t, $C_{5,7}$), 25.67(t, C_6), 29.88(t, $C_{2,10}$), 52.61(q, $-OCH_3$), 56.46(s, C_1), 124.31(d, $C_{3,9}$), 133.30 (d, $C_{4,8}$), and 171.68(s, C=O); m/e 252(M^+). On double irradiation of the proton multiplet at δ5.11, the multiplets at 2.40 and 2.80 collapsed to a slightly broadened AB quartet, J_{AB} = 14.0Hz.

14. A single 2:2 adduct (m/e 504) was also isolated in 18% yield and has tentatively been identified as i,[7] primarily on the basis of the ^1H NMR spectrum ($CDCl_3$, 250MHz): δ1.39(m, 4H, $-CH_2\underline{CH_2}CH_2-$), 2.03(m, 8H, $=CHCH_2\underline{CH_2}-$), 2.61(m, 8H, $=CHCH_2C(CO_2CH_3)_2$), 3.72(s, 12H, $-OCH_3$), 5.22(m, 4H, $=CHCH_2C(CO_2CH_3)_2$), and 5.50(m, 4H, $=CHCH_2CH_2-$). Double irradiation of the multiplet at δ5.22 led to collapse of the multiplet at δ2.61 to a singlet. No 2:2 adduct was detected in the formation of 8.



i

15. J.J. Tufariello and W.J. Kissel, Tetrahedron Lett., 6145(1966).

16. Cf., R.A. Ruden and R. Bonjouklian, J. Am. Chem. Soc., 97, 6892(1975).

17. K. Ogura, M. Yamashita, S. Furukawa, M. Suzuki and G. Tsuchiahashi, Tetrahedron Lett., 2767(1975).

18. (a) O. Possel and A.M. van Leusen, Tetrahedron Lett., 4229(1977): (b) D. van Leusen and A.M. van Leusen, Synthesis, 325(1980).

19. IR(CCl_4): 1700(s), 1640(w), and 1445(m) cm^{-1}; ^1H NMR($CDCl_3$, 250MHz): δ1.70(2H, quintet, J = 5.5Hz, $-CH_2\underline{CH_2}CH_2-$), 2.16(4H, dt, J = 5.5, 7.0Hz, $=CHCH_2\underline{CH_2}-$), 3.13(4H br s, $-\underline{CH_2}CO-$), and 5.49(4H, m, $-\underline{CH}=\underline{CH}-$); ^{13}C NMR($CDCl_3$, 62.9MHz): δ24.84(t, $-\underline{CH_2}CH_2\underline{CH_2}-$), 25.84(t, $-CH_2\underline{CH_2}CH_2-$), 41.66(t, $-\underline{CH_2}COCH_2-$), 122.81(d, $-COCH_2\underline{CH}=$), 133.69(t, $-CH_2CH_2\underline{CH}=$), and 208.56(s, C=O); m/e 150(M^+).

(Received in USA 10 November 1980)