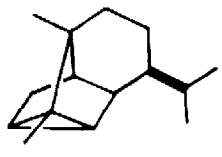
Tetrahedron Letters Vol. 21, pp 4707 - 4710 0040-4039/80/1201-4707$02.00/0

SYNTHESIS WITH BENZENESULFENYL CHLORIDE
A NEW WAY TO CYCLOSATIVENE

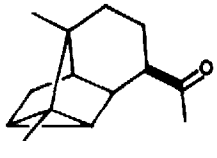
Denis HEISSLER[1] and Jean-Jacques RIEHL
Institut de Chimie, Université Louis Pasteur
BP 296/R8 - 67008 STRASBOURG (FRANCE)

ABSTRACT: *The total synthesis of the tetracyclic methylketone 2, a synthetic precursor of cyclosativene 1, is reported. The tricyclene ring system of 2 is obtained by the electrophilic addition of benzenesulfenyl chloride to a suitably substituted methylenenorbornene 7. Closure of the fourth ring is achieved by intramolecular acylation of an α-alkylated sulfone.*

The intricate molecular structure of the tricyclene related sesquiterpene cyclosativene 1 [2] has attracted the attention of several research groups and three syntheses of this compound have been reported so far[3-5].

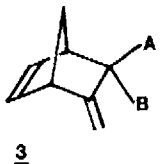


Cyclosativene 1



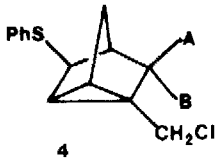
2

Tricyclene



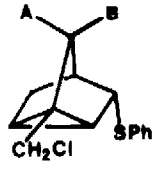
3

PhSCl



4

≡



We have recently shown that functionalized tricyclenic compounds 4 can be obtained by the electrophilic addition of benzenesulfenyl chloride to methylenenorbornenes 3[6]. In this letter, we wish to describe an application of this reaction to the total synthesis of the tetracyclic methylketone 2, which can be transformed into cyclosativene by a Wittig reaction ($Ph_3P{=}CH_2$) followed by a catalytic hydrogenation ($(Ph_3P)_3$ RhCl, H_2)[7].

The starting material chosen for the synthesis of 2 is the ditosylate 5 which is readily available, in three steps, from cyclopentadiene and citraconic anhydride [8]. Sequential treatment of the ditosylate 5 in HMPA, with anhydrous lithium bromide (6 equiv., 120°C, 4 h) and with sodium cyanide (10 equiv., 120°C, 12 h) afforded the nitrile 7, *via* the bromide 6,

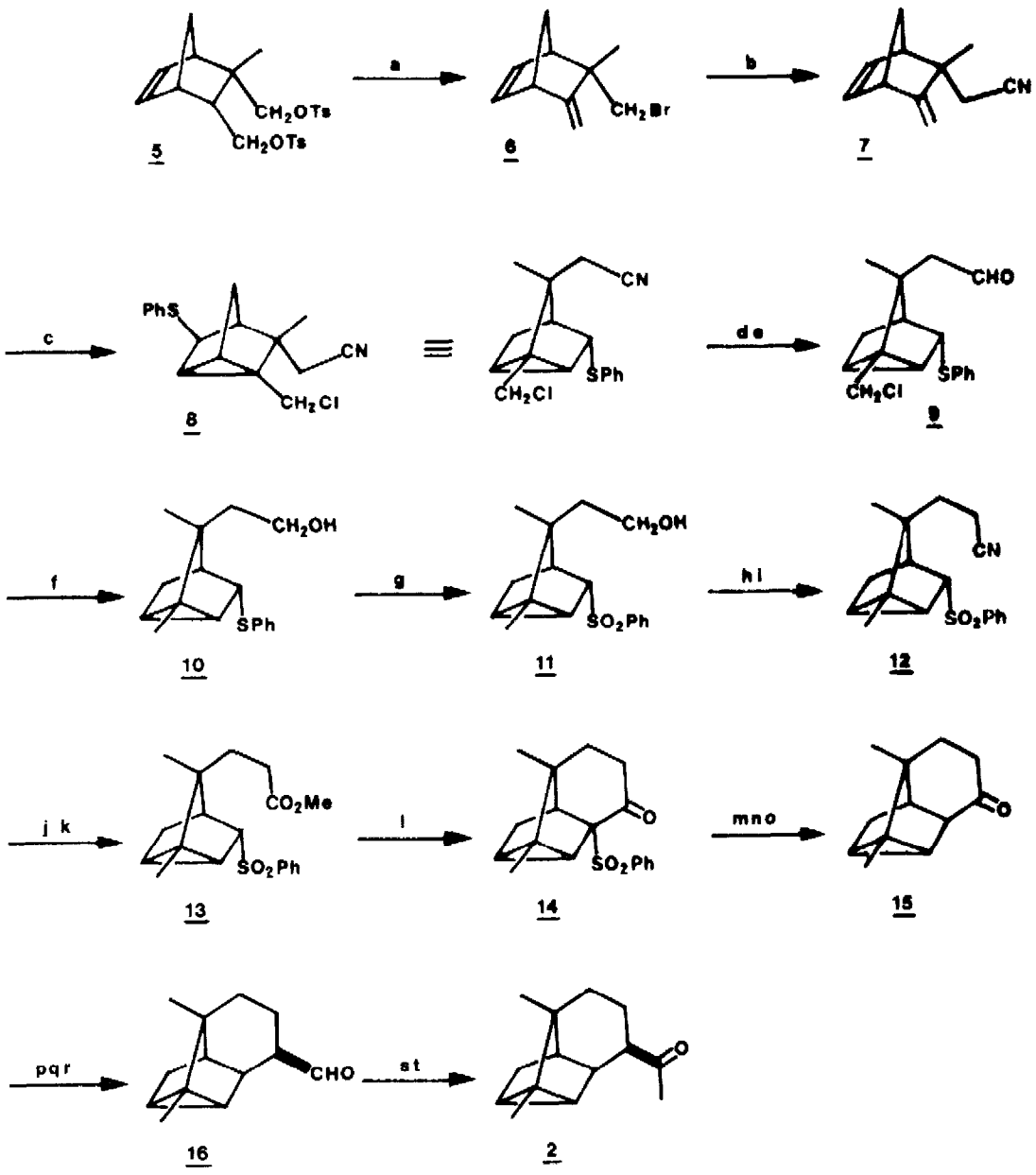
in a one-pot procedure (89 % yield). The nitrile 7 was then allowed to react with benzenesulfenyl chloride[9] (1.1 equiv., CH_2Cl_2, 0°C) to furnish the tricyclenic compound 8 in 85 % yield. Reduction of 8 with diisobutylaluminum hydride[10] (1.1 equiv., benzene, 10°C → r.t., 1 h) followed by hydrolysis (10 % aqueous H_2SO_4, 10°C, 1h) gave a 77 % yield of the aldehyde 9 which was reduced to compound 10 with lithium triethylborohydride [11] (6 equiv., THF, r.t., 18 h, 94 % yield).

After obtention of the tricyclenic hydroxy sulfide 10, we planned to take advantage of its phenylthio substituent to convert 10 into the tetracyclic ketone 15. It was assumed that, after transformation of 10 into the tricyclic carbomethoxy sulfone 13, suitable base treatment of this latter compound followed by reductive cleavage of the expected β-keto sulfone 14, would yield the tetracyclic ketone 15. The carbonyl group of this ketone 15 should then serve as a "handle" for the introduction of the additional two carbon atoms necessary to complete the skeleton of the target compound 2.

The conversion of the hydroxy sulfide 10 into the carbomethoxy sulfone 13 was carried out as follows. Oxidation of 10 with m-chloroperbenzoic acid (2.2 equiv., CH_2Cl_2) gave a nearly quantitative yield of hydroxy sulfone 11. Mesylation of 11 (MsCl, NEt_3, CH_2Cl_2, 0°C)[12] followed by treatment with sodium cyanide (5 equiv., 1:1 THF-DMSO, reflux, 16 h) led to the cyano sulfone 12 (88 % yield) which was transformed into the carbomethoxy sulfone 13 (87 % yield) by a Pinner synthesis [13] (dry HCl, methanol, THF, 0°C/ 1h , r.t./1 h) followed by an acid hydrolysis.

Conversion of the α-alkylated carbomethoxy sulfone 13 into the desired tetracyclic β-keto sulfone 14 required a Dieckmann type condensation[14]. After extensive investigation, we found that this condensation could be accomplished efficiently by treatment of compound 13 with potassium bis(trimethylsilyl)amide[15] (5 equiv., THF, r.t., 2 h) followed by quenching with acetic acid at -78°C (78 % yield). The β-keto sulfone 14 was then transformed into the ketone 15 (71 % yield) by reduction ($LiAlH_4$, THF), reductive cleavage (Li, $EtNH_2$, THF, -78°C)[16] and oxidation (CrO_3-2py, CH_2Cl_2)[17]. Use of other procedures (aluminum amalgam, THF - water or zinc dust, ethanol-acetic acid)[18, 19] proved unsatisfactory. Finally, treatment of 15 with methoxymethylenetriphenylphosphorane in DMSO [20, 21] followed by hydrolysis (35 % aqueous $HClO_4$, ether, 45 min) and epimerization (dry K_2CO_3, methanol, 3h) produced aldehyde 16 in 43 % yield. Upon treatment of 16 with methyllithium in ether followed by oxidation (CrO_3-2py), we obtained in 60 % yield, a ketone which was identified (IR, 60 MHz NMR) as methylketone 2 [7].

ACKNOWLEDGMENT : We are very grateful to Professor J. Ficini for a fruitful discussion and to Professor A. Yoshikoshi for the IR and 60 MHz NMR spectra of ketones 15 and 2 .



a) LiBr, HMPA, 120°C ; b) NaCN, HMPA, 120°C (5 → 7 : 89 % yield) ; c) PhSCl, CH_2Cl_2, 0°C (85 %); d) $(i\text{-}Bu)_2$ AlH, benzene ; e) 10 % aqueous H_2SO_4 (8 → 9 : 77 %) ; f) $LiBHEt_3$, THF (94 %) ; g) m-CPBA, CH_2Cl_2 (99 %) ; h) MsCl, NEt_3, CH_2Cl_2 ; i) NaCN, THF, DMSO (11 → 12 : 88 %) ; j) dry HCl, MeOH, THF ; k) H_3O^+ (12 → 13 : 87 %) ; l) $KN(SiMe_3)_2$, THF (78 %) ; m) $LiAlH_4$, THF ; n) Li, $EtNH_2$, THF, -78°C ; o) CrO_3-2py, CH_2Cl_2 (14 → 15 : 71 %) ; p) $Ph_3P{=}CHOCH_3$, DMSO ; q) 35 % aqueous $HClO_4$, ether ; r) K_2CO_3, MeOH (15 → 16 : 43 %) ; s) MeLi, ether ; t) CrO_3-2py, CH_2Cl_2 (16 → 2 : 60 %).

REFERENCES AND NOTES

1) Centre National de la Recherche Scientifique.

2) L. SMEDMAN, E. ZAVARIN, Tetrahedron Lett. 3833 (1968) ; L.A. SMEDMAN, E. ZAVARIN, R. TERANISHI, Phytochemistry 8, 1457 (1969)

3) J.E. Mc MURRY, Tetrahedron Lett. 55 (1969) ; J.E. Mc MURRY, J. Org. Chem. 36, 2826 (1971)

4) E. PIERS, M.B. GERAGHTY, M. SOUCY, Synth. Commun. 3, 401 (1973) ; E. PIERS, R.W. BRITTON, M.B. GERAGHTY, R.J. KEZIERE, R.D. SMILLIE, Can. J. Chem. 53, 2827 (1975) ; E. PIERS, M.B. GERAGHTY, R.D. SMILLIE, M. SOUCY, Can. J. Chem. 53, 2849 (1975)

5) S.W. BALDWIN, J.C. TOMESCH, Tetrahedron Lett. 1055 (1975) ; S.W. BALDWIN, J.C. TOMESCH J. Org. Chem. 45, 1455 (1980)

6) D. HEISSLER, J.J. RIEHL, Tetrahedron Lett. 3957 (1979); see also N.S. ZEFIROV, N.K. SADOVAJA, R.SH. ACHMEDOVA, I.V. BODRIKOV, Zh. Org. Khim. 15, 217 (1979); Chem. Abst.90, 203614j (1979)

7) F. KIDO, R. SAKUMA, H. UDA, A. YOSHIKOSHI, Tetrahedron Lett. 3169 (1969)

8) D. HEISSLER, F. JUNG, J.P. VEVERT, J.J. RIEHL, Tetrahedron Lett. 4879 (1976)

9) Prepared according to F.G. BORDWELL; M. FIESER and L.F. FIESER,"Reagents for Organic Synthesis", Vol 5, p. 523, John Wiley and Sons, Inc., New York (1975)

10) L.I. ZAKHARKIN, I.M. KHORLINA, Dokl. Akad. Nauk SSSR 116, 422 (1957) ; Chem. Abst. 52, 8040f (1958)

11) H.C. BROWN, S. KRISHNAMURTHY, J. Am. Chem. Soc. 95, 1669 (1973)

12) R.K. CROSSLAND, K.L. SERVIS, J. Org. Chem. 35, 3195 (1970)

13) Reviews :
- E.N. ZIL'BERMAN, Russ. Chem. Rev. 31, 615 (1962)
- P.L. COMPAGNON, M. MIOCQUE, Ann.Chim. (Paris) 5, 23 (1970)

14) G. NEE, B. TCHOUBAR, Tetrahedron Lett. 3717 (1979)

15) Prepared according to C.A. BROWN, J. Org. Chem. 39, 3913 (1974)

16) W.E. TRUCE, D.P. TATE, D.N. BURDGE, J. Am. Chem. Soc. 82, 2872 (1960)

17) R. RATCLIFFE, R. RODEHORST, J. Org. Chem. 35, 4000 (1970)

18) E.J. COREY, M. CHAYKOVSKY, J. Am. Chem. Soc. 87, 1345 (1965)

19) G.A. RUSSELL, G.J. MIKOL, J. Am. Chem. Soc. 88, 5498 (1966)

20) S.G. LEVINE, J. Am. Chem. Soc. 80, 6150 (1958)

21) R. GREENWALD, M. CHAYKOVSKY, E.J. COREY, J. Org. Chem. 28, 1128 (1963)

(Received in France 1 September 1980)