A Novel Route to Substituted Cyclopent-2-en-1-one; Application to the Synthesis of cis-Jasmone and Dihydrojasmone†

Jacob Mathew*‡ and Ben Alink

Petrolite Corporation, 369 Marshall Avenue, St. Louis, Mo 63119, USA

A short and efficient synthesis of cis-jasmone and dihydrojasmone has been achieved by the reaction of sulphur-stabilized carbanions with ethyl 2-chloro-2,3-dialkylbut-3-enoates.

There has been considerable interest in the synthesis and biological properties of relatively simple compounds such as prostanoids, jasmonoids, and methylenomycins which incorporate the cyclopentenone unit.[1] The most versatile syntheses of cyclopentenones involve the initial preparation of acylic 1,4-dicarbonyl compounds[2,3] and their subsequent intramolecular base-catalysed aldol condensation. Although a variety of other routes based on dioxocyclopentanes[4,5] and cyclodehydration of γ-lactones[6] have been reported, most of these routes are either too lengthy or involve the use of expensive chemicals.[7] A relatively efficient route to functionally substi-

tuted cyclopentenones involves an intramolecular Wittig reaction effected by the treatment of the anion of α-diketones with vinyl triphenylphosphonium salts.[8]

We have now found that substituted cyclopent-2-enones can be synthesized by the reaction of sulphur-stabilized carbanions with ethyl 2-chloro-2,3-dialkylbut-3-enoates.[9] These functionalized allylic chlorides are in turn prepared by the reaction of substituted acrylic esters with hypochlorous acid generated using calcium hypochlorite/acetic acid[10] (Scheme 1).§

Reaction of (1) with sulphur-stabilized carbanions under mild conditions gave good yields (~70%) of cyclopentenones directly. Lithio-1,3-dithiane,[11] lithiobis(phenylthio)methane[12] and lithio(phenylthio)methane[13] can be used as the nucleophile. A two-step mechanism is postulated for this
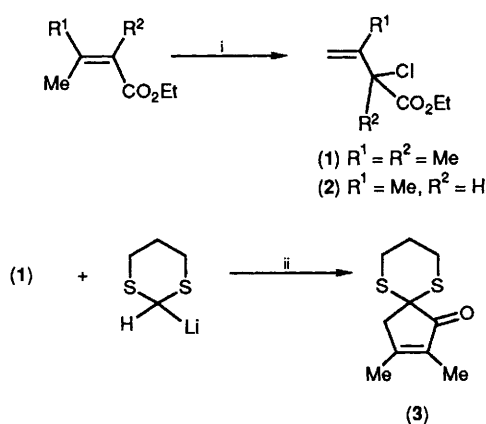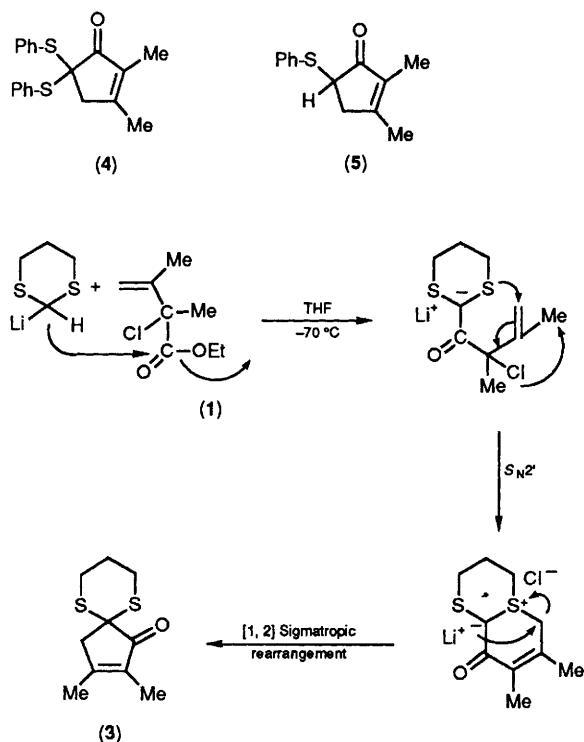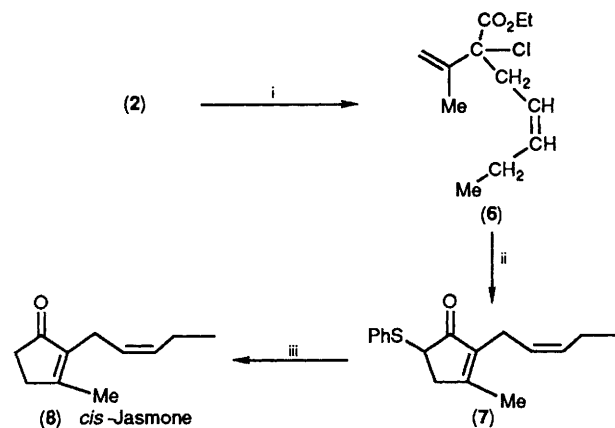

Scheme 1. *Reagents and conditions*: i, $Ca(OCl)_2$, AcOH, CH_2Cl_2, 62—80%; ii, THF–tetramethylethylenediamine (TMEDA), $-70\,°C$ to room temp., 70%.

Scheme 3. *Reagents and conditions*: i, $KN(SiMe_3)_2$, THF, hexamethyl-phosphoric triamide (HMPA); $EtCH=CHCH_2OSO_2C_6H_4Me$-p, 78%; ii, $PhSMe$-Bu^nLi-TMEDA, THF, 46%; iii, Raney nickel, Me_2CO, 88%.

Scheme 2

Scheme 4. *Reagents and conditions*: i, $KN(SiMe_3)_2$, THF, HMPA, Bu^nCH_2I, 70%; ii, $PhSMe$-Bu^nLi-TMEDA, THF, 42%; iii, Raney nickel, Me_2CO, 92%.
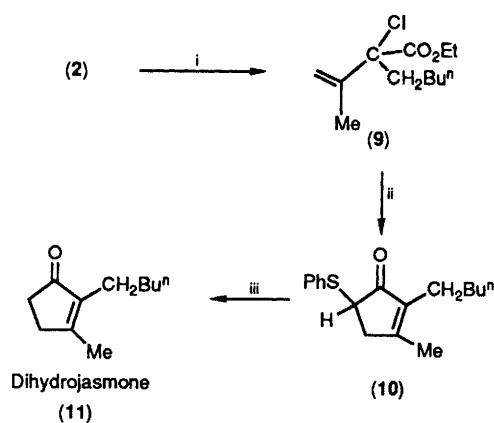
one-pot reaction and is shown for lithio-1,3-dithiane in Scheme 2.

The first step is an acylation by 2-lithio-1,3-dithiane with (1) to give an intermediate keto-dithiane enolate followed by a novel variation of an intramolecular abnormal S_N2 reaction.[14] It is proposed that the second step is through a sulphur-assisted S_N2' reaction. The final process is an intramolecular attack by sulphur on the allylic carbon to give a stable sulphonium ylide followed by a [1,2] sigmatropic rearrangement[15] to give the observed product. Ylide formation during alkylation of selenium and sulphur substituted enolates has

been well documented.[16] However, the ylides usually undergo [2,3] sigmatropic rearrangement. Ylide formation and subsequent [2,3] sigmatropic shift has been observed in the alkylation of unsymmetrical allylic halides with 2-lithio-2-formyl-1,3-dithiane but in this case the first step involves a normal S_N2 attack by the sulphur atom.[17] To our knowledge this is the first example reported for such a transformation involving a stable sulphur ylide.

The synthetic implications of this transformation are appealing since desulphurization gave disubstituted cyclopentenones. Whereas compounds (4) and (5) undergo desulphurization with Raney nickel (Aldrich) at room temperature almost instantaneously and quantitatively, compound (3) requires drastic reaction conditions and gives lower yield. Among the three sulphur-stabilized nucleophiles that we have examined, lithio(phenylthio)methane is the preferred reagent, owing to its ready availability and the ease of removal of sulphur to form the cyclopentenones. In order to demonstrate the versatility of this reaction we have completed a short (three-step) synthesis of dihydrojasmone[18] (11) and *cis*-jas-

mone[19] (8), the odorous principle of jasmine flowers (Schemes 3 and 4).¶

A common feature of both the schemes involves the high-yield alkylation of ethyl 2-chloro-3-methylbut-3-enoate (2) to give the highly substituted allylic chlorides (6) and (9). Attempts to prepare these from suitably substituted acrylates using hypochlorous acid were not successful. The present method is synthetically useful since it allows the introduction of different substituents at the α-carbon of these esters. Although the deconjugative alkylation of dialkyl substituted acrylates has been reported,[20] the deconjugative alkylation of 2-halogeno-3,3-dimethylbut-2-enoate has not been successful since halogen–metal exchange is often observed.[21] We did not encounter such a problem during alkylation of (2) presumably owing to the high kinetic acidity of the hydrogen atoms on the allylic carbon atom bearing the halogen and ester group.

The commercially available cis-pent-2-en-1-ol can be converted to the corresponding cis-tosylate[22] in high yield using powdered NaOH in tetrahydrofuran (THF) and tosyl chloride at 0 °C. The crude cis-tosylate was used immediately for the alkylation. Attempts to convert cis-pent-2-en-1-ol to the bromide using either PBr_3 or $NaBr/BF_3$ were not successful since rearranged products were formed.[23] The yields of (7) and (10) have not been optimized and studies are underway to increase the yields.

Addendum: Since submission of this communication, we have found that nitrogen-stabilised carbanions undergo this type of cyclisation at −78 °C. There is strong evidence that this is not a simple abnormal S_N2 reaction but that the reaction proceeds through heteroatom assistance. Details of this will be published shortly. We are merely suggesting that [1,2] sigmatropic shift is a plausible mechanistic explanation for the observed result. Prof. Barry Trost (Stanford) informs us that he had discussed the prospect of initial reaction at sulphur followed by ylide rearrangement (*J. Am. Chem. Soc.*, 1977, **99**, 3101).

Received, 20th November 1989; Com. 9/04957F

¶ *Spectral data* for (6): ^{1}H NMR, δ 5.40 (m, 2H), 5.25 (s, 1H), 5.10 (s, 1H), 4.20 (q, 2H), 2.90 (t, 2H), 2.10 (q, 2H), 1.85 (s, 3H), 1.25 (t, 3H), and 0.95 (t, 3H); ^{13}C NMR, δ 169.46, 142.19, 135.31, 122.01, 114.66, 75.19, 62.33, 36.23, 21.03, 19.60, and 14.02; IR (neat), $v_{max.}$ 3050, 2900, and 1740 cm^{-1}.

For (7): ^{1}H NMR, δ 7.30 (m, 5H), 5.30 (m, 2H), 3.70 (d of d, 1H), 2.90 (d, 2H), 2.4—2.6 (m, 2H), 2.10 (q, 2H), 2.00 (s, 3H), and 1.00 (t, 3H); ^{13}C NMR δ 204.14, 168.43, 138.43, 132.58, 131.93, 128.69, 127.43, 124.40, 47.52, 40.51, 21.42, 20.51, 17.01, and 14.15; IR (neat), $v_{max.}$ 2950, 1700, and 1650 cm^{-1}.

For (9): ^{1}H NMR, δ 5.40 (s, 1H), 5.20 (s, 1H), 4.35 (q, 2H), 2.30 (m, 2H), 2.00 (s, 3H), 1.45 (m, 9H), and 1.05 (t, 3H); ^{13}C NMR, δ 169.72, 142.45, 114.40, 76.22, 62.07, 38.17, 31.68, 29.15, 22.46, 19.35, and 13.89.

For (10): ^{1}H NMR, δ 7.50 (m, 5H), 3.90 (d of d, 1H), 2.70—3.30 (m, 2H), 2.30 (m, 2H), 2.15 (s, 3H), 1.40 (m, 6H), and 1.00 (t, 3H); ^{13}C NMR, δ 205.20, 168.04, 139.73, 132.06, 128.69, 127.39, 47.65, 40.38, 31.68, 27.78, 23.29, 22.44, 17.01, and 14.02.

Satisfactory elemental analyses were obtained for (6), (7), and (9)—(11).

References

1 G. Casy and R. J. K. Taylor, *J. Chem. Soc., Chem. Commun.*, 1988, 484; J. D. Elliot, M. Hetmanski, R. J. Stoodley, and M. N. Palfreyman, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1782; M. Koreeda and Y. P. Liang, *Tetrahedron Lett.*, 1981, **22**, 15; Y. Takahashi, K. Isobe, H. Hagiware, H. Kosugi, and H. Uda, *J. Chem. Soc., Chem. Commun.*, 1981, 714, and references cited therein.

2 For a review on synthetic approaches to cyclopentenones, see R. A. Ellison, *Synthesis*, 1973, 397.

3 M. Miklojczyk, S. Grzejsczak, and K. Korbacz, *Tetrahedron Lett.*, 1981, **22**, 3097; M. Miklojczyk, S. Grzejsczak, and P. Kyzwa, *ibid.*, 1982, **23**, 2237; J. L. Herrman, J. E. Richmann, and R. H. Schlessinger, *ibid.*, 1973, 3275; P. Bakuzis and M. L. F. Bakuzis, *J. Org. Chem.*, 1977, **42**, 2362; S. C. Subramaniam, P. J. Thomas, V. R. Mamdapur, and M. S. Chadha, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2346.

4 Y. Yura and J. Ide, *Chem. Pharm. Bull*, 1969, **17**, 408.

5 J. L. E. Erickson and F. E. Collins, Jr., *J. Org. Chem.*, 1965, **30**, 1050.

6 K. Sisido, S. Torji, and M. Kawanisi, *J. Org. Chem.*, 1964, **29**, 904.

7 For a short and efficient route to cis-jasmone, see G. Buchi and B. Egger, *J. Org. Chem.*, 1971, **36**, 202; for a recent approach based on enol phosphate, see S. C. Welch, J. N. Assercq, J. P. Loh, and S. A. Glase, *ibid.*, 1987, **52**, 1440.

8 A. G. Cameron and A. T. Hewson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2979; I. Kawamoto, S. Muramatsu, and Y. Yura, *Tetrahedron Lett.*, 1974, 4223.

9 A systematic study of the reaction of these functionalized allylic chlorides with various nucleophiles will be reported shortly.

10 For deconjugative chlorination of: substituted α,β-unsaturated ketones, see S. G. Hedge and J. Wolinksy, *Tetrahedron Lett.*, 1981, **22**, 5019; α-alkylidene β-lactams, see J. D. Buynak, J. Mathew, M. N. Rao, E. Haley, C. George, and U. Shriwardane, *J. Chem. Soc., Chem. Commun.*, 1987, 735.

11 D. Seebach and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231.

12 E. J. Corey and D. Seebach, *J. Org. Chem.*, 1966, **31**, 4097.

13 D. J. Ager, *J. Chem. Soc., Perkin. Trans. 1*, 1983, 1131, and references therein.

14 G. Stork and A. F. Kreft, *J. Am. Chem. Soc.*, 1977, **99**, 3851; for a recent review on S_N2' reactions, see R. M. Magid, *Tetrahedron*, 1980, **36**, 1901.

15 R. H. Mitchess and V. Boekelheide, *J. Am. Chem. Soc.*, 1974, **96**, 1547; for examples of [1,2] sigmatropic shifts of stabilized sulphonium ylides, see E. Block, 'Reactions of Organosulfur Compounds,' Academic Press, New York, 1978, p. 118.

16 H. J. Reichs and M. L. Cohen, *J. Am. Chem. Soc.*, 1979, **101**, 1307.

17 S. R. Wilson and J. Mathew, *Synthesis*, 1980, 625.

18 Identical in all respects with reported spectroscopic data: P. A. Grieco, *J. Org. Chem.*, 1972, **37**, 2363; T. Mukaiyama, K. Narasaka, and M. Farasoto, *J. Am. Chem. Soc.*, 1972, **94**, 8641.

19 Identical in all respects with reported spectroscopic data: L. Crombie, P. Hemesley, and G. Pattenden, *J. Chem. Soc.*, 1969, **6**, 1024, and ref. 3.

20 B. Ha, D. J. Hart, and T. K. Yang, *J. Am. Chem. Soc.*, 1984, **106**, 4819; J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 1973, 2433.

21 W. E. Parham and D. W. Boykin, *J. Org. Chem.*, 1977, **42**, 260.

22 This tosylate has been previously synthesized; however experimental details were not reported. See G. Stork and R. Borch, *J. Am. Chem. Soc.*, 1964, **86**, 936.

23 A. K. Mandal and S. W. Mahajan, *Tetrahedron Lett.*, 1985, **26**, 3863.