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A PRACTICAL SYNTHESIS OF TRANS-IODOOLEFINS

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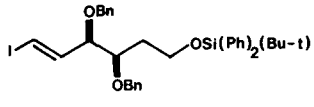
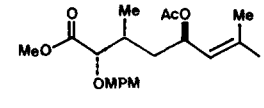
Abstract: Trimethylsilyl iodide was found to react smoothly with the acetylenic ketones 3 and 6 to yield the trans-β-iodovinyl ketones 4 and 7, respectively. Hydride reduction of 4 and 7 gave the trans-iodoolefins 5 and 8, which correspond to the C.19-C.22 and C.1-C.7 portions of the marine natural product palytoxin.

During the synthetic studies on the marine natural product palytoxin,[1-3] we needed to synthesize di- and tri-substituted iodoolefins such as 1 and 2.[4] In spite of substantial efforts, we were unable to apply any iodoolefin synthesis known in the literature to prepare 1 and 2 in large scale in a satisfactory chemical yield.[5] Thus, we have searched for a practical solution to this problem and found that the reaction of trimethylsilyl iodide with an acetylenic ketone provides an easy entry to this type of iodoolefin.



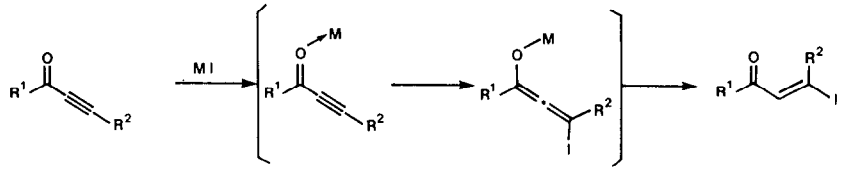
1



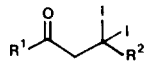
2

β-Iodovinyl ketones[6] appeared to be the promising precursors to the requisite iodoolefins. In principle, they should be obtainable from the corresponding acetylenic ketones via a Michael reaction. However, to the best of our knowledge, Michael addition of iodide anion to an acetylenic ketone is not a highly practical synthetic process.[7] We hoped that this difficulty might be overcome by activating the carbonyl group of the acetylenic ketone in the presence of iodide anion or its equivalent, i.e. i → ii → iii → iv (Scheme 1). Trimethylsilyl iodide (TMSI) is obviously one of the reagents which meets this requirement.[8]

Scheme 1



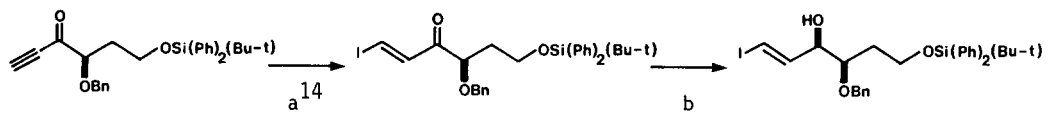
i ii iii iv



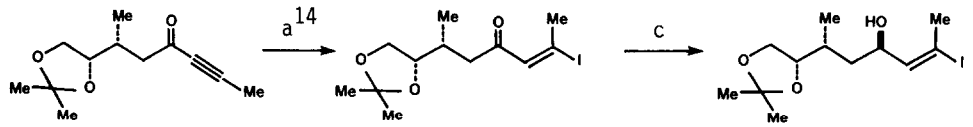
v

Indeed, TMSI smoothly reacted with acetylenic ketones 3 and 6 to yield the desired trans-β-iodovinyl ketones 4 and 7, respectively (Scheme 2). When excess TMSI (>1.2 eq) was used, the formation of β,β-diiodoketone was observed. However, this was not a problem from a practical viewpoint since base treatment [$(i\text{-}Pr)_2(Et)N/CH_2Cl_2$/RT/2 hr] of v yielded the corresponding β-iodovinyl ketone. In connection with the sequence shown in Scheme 1, it is interesting to note that iii (M=TMS) is unstable but detectable by NMR spectroscopy. As might be expected, this process provided a trans-iodovinyl ketone as the major product; the stereoselectivity of 3 → 4 was at least 20:1 favoring 4 over its cis-isomer, and the stereoselectivity of 6 → 7 was 7:2 favoring 7 over its cis-isomer. In addition, as base treatments [$(i\text{-}Pr)_2(Et)N/CH_2Cl_2$/RT/overnight] of β-iodovinyl ketones regenerate acetylenic ketones, either Z- or E-β-iodovinyl ketones can be recycled.

Scheme 2



3[12,13] 4 5



6[12] 7 8

Reagents and Conditions

a. TMSI (ca. 1.8 eq)/CH_2Cl_2/-78°C, followed by $(i\text{-}Pr)_2(Et)N/CH_2Cl_2$/RT/2 hr.[14]

b. $LiBH_4/TbCl_3 \cdot 6H_2O$/MeOH/0°C.

c. $LiAlH_4$/2S,3R-Darvon alcohol/Et_2O/-78°C.

Functional group manipulation of the β-iodovinyl ketones thus obtained did not present any difficulty. For example, $LiBH_4/TbCl_3$ reduction[3a] of 4 yielded a 5:1 mixture of the two possible diastereomers favoring the threo isomer 5 as anticipated from the Cram's cyclic transition state model.[9] Asymmetric reduction was also effective for these compounds; reduction of 7 with $LiAlH_4$/2S,3R-Darvon alcohol[10,11] yielded a 5:1 mixture of 8 and its stereoisomer.

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References and Footnotes

1. For the gross structure of palytoxin, see: (a) D. Uemura, K. Ueda, Y. Hirata, H. Naoki, and T. Iwashita, Tetrahedron Lett., 22, 2781 (1981) and references cited therein. (b) R. E. Moore and G. Bartolini, J. Am. Chem. Soc., 103, 2491 (1981) and references cited therein. For the structures of minor constituents, see D. Uemura, Y. Hirata, T. Iwashita, and H. Naoki, Tetrahedron, 41, 1007 (1985).

2. For the stereochemistry assignment primarily based on organic synthesis, see J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, Y. Kishi, L. L. Klein, S. S. Ko, J. Leder, W. W. McWhorter, Jr., K.-P. Pfaff, M. Yonaga, D. Uemura, and Y. Hirata, J. Am. Chem. Soc., 104, 7369 (1982) and preceding papers. For the stereochemistry assignment primarily based on spectroscopic methods, see R. E. Moore, G. Bartolini, J. Barchi, A. A. Bothner-By, J. Dadok, and J. Ford, J. Am. Chem. Soc., 104, 3776 (1982).

3. For synthetic studies on palytoxin, see: (a) Y. Kishi, W. J. Christ, and M. Taniguchi, "Natural Products and Biological Activities", ed. H. Imura, T. Goto, T. Murachi, and T. Nakajima, University of Tokyo Press, Tokyo, 1986, p. 87 and references cited therein. (b) W. C. Still and I. Galynker, J. Am. Chem. Soc., 104, 1774 (1982).

4. These iodoolefins were used for Cr(II)-mediated coupling reactions; see: (a) references cited in 3a. (b) H. Jin, J.-I. Uenishi, W. J. Christ, and Y. Kishi, submitted for publication.

5. Trans-iodoolefin 1 was originally prepared by catechol hydroboration of an acetylene, followed by I_2/NaOH treatment. This process was excellent in terms of stereochemical control, but the chemical yield of the iodination step was 65% at best in our hands.

6. There are a number of β-iodovinyl ketones known in the literature, but only a few synthetic methods are available for these compounds. These include: 1. a route via β-chlorovinyl ketones [E. J. Corey and B. J. Beames, J. Am. Chem. Soc., 94, 7210 (1972)], 2. a route via β-diketones [E. Piers, J. R. Grierson, C. K. Lau, and I. Nagakura, Can. J. Chem., 60, 210 (1982)], and 3. a route via 1-iodo-2-trimethylsilyl ethylene [J.-P. Pillot, J. Dunogues, and R. Calas, Synth. Commun., 9, 395 (1979)].

7. Michael addition of HI to propiolic acid is known; see K. Bowden and M. J. Price, J. Chem. Soc. (B), 1466 (1970) and references cited therein. Also see M. E. Jung, J. A. Hagenah, and L.-M. Zeng, Tetrahedron Lett., 24, 3973 (1983).

8. TMSI is known to react with α,β-unsaturated ketones to yield β-iodoketones; see R. D. Miller and D. R. McKean, Tetrahedron Lett., 2305 (1979).

9. For a review on this subject, see, for example, J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," American Chemical Society, Washington, D.C., 1976.

10. For reviews on this subject, see, for example, "Asymmetric Synthesis, Vol. 2" ed. J. D. Morrison, Academic Press, New York, 1983.

11. R. S. Brinkmeyer and V. M. Kapoor, J. Am. Chem. Soc., 99, 8339 (1977).

12. The synthesis of this substance will be detailed in a full paper.

13. Satisfactory spectroscopic data were obtained for all the new compounds in this paper.

14. The following is a representative procedure for the β-iodovinyl ketone preparation. To a methylene chloride solution of 3 (10.97 g/100 ml) was added TMSI (6.2 ml, ca. 1.8 eq) dropwise at -78°C under argon atmosphere. After the addition was complete, the mixture was stirred at -78°C for about 10 min, quenched by adding Et_2O-H_2O at -78°C, and allowed to warm up to ca. 5°C. The reaction mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, aq. Na_2SO_3, brine, and dried over $MgSO_4$. After $MgSO_4$ was removed by filtration, $(i\text{-}Pr)_2(Et)N$ (10 ml) was added to the filtrate (ca. 300 ml) slowly. The reaction mixture was stirred at room temperature for 2 hours, washed with 1N HCl, sat. $NaHCO_3$, and brine, and dried over $MgSO_4$. After $MgSO_4$ was removed by filtration, the filtrate was concentrated under reduced pressure to give 13.43 g (96% yield) of crude 4 contaminated with less than 5% of the cis-iodovinyl ketone. The crude product was of satisfactory purity for use in the next reduction. If needed, the pure β-iodovinyl ketone was obtained by silica gel column chromatography.

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