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GENERAL ROUTE TO α,β-UNSATURATED ALDEHYDES OF HOMOTERPENOID AND TERPENOID STRUCTURE. SYNTHESIS OF JH-II AND β-SINENSAL

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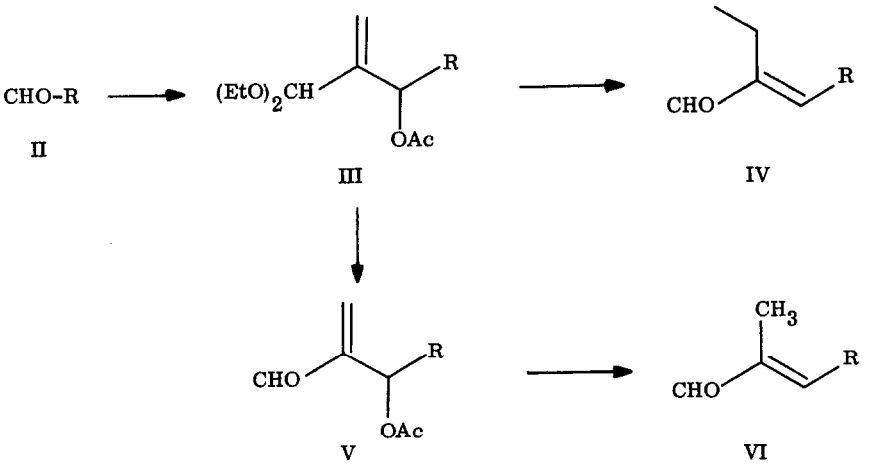
According to the procedure described in the previous communication[1] 2-substituted propenal derivatives are readily available from 1-bromo-2-ethoxycyclopropyllithium (I) and electrophiles. Starting with aldehyde II we can easily obtain the product of type III which is now disclosed to be a particularly useful common intermediate for the synthesis of α,β-unsaturated aldehyde moiety of homoterpenoid (IV) and terpenoid (VI) structure.

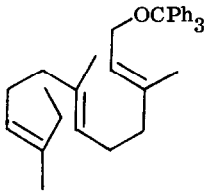


a: R = n-C_6H_{13}

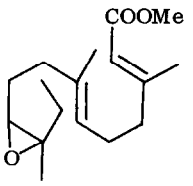
b: R = $CH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2OCPh_3$

c: R = $CH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_2)CH=CH_2$

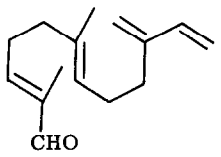
Treatment of heptanal with 1.2 mol of I generated from 1,1-dibromo-2-ethoxycyclopropane and butyllithium at -95°, followed by ring cleavage of the resulting adduct (5 mol of potassium carbonate, ethanol (reflux), 1 hr) and acetylation (acetic anhydride-pyridine, r.t., overnight), gave IIIa[2,3] in 80% yield after purification by column chromatography (silica gel). The allylic acetate IIIa was treated with 1.5 mol of dimethylcopperlithium in ether at -18°[4] for 30 min to give, after acid-hydrolysis (5% aq sulphuric acid-ether, r.t., 5 min) of the acetal function, (E)2-ethyl-2-nonenal (IVa)[5,6] in 61% yield. Selective S_N2' type methyl introduction is the key of the present synthesis. With this result in hand we soon applied the reaction to the synthesis of juvenile hormone (JH-II).[7] Addition of the carbenoid of I to an aldehyde IIb[8] and the subsequent two-step transformation of the adduct as above afforded IIIb[9] in 84% overall yield, which was further treated with 4 mol of dimethylcopperlithium and then with 5% aq sulphuric acid in tetrahydrofuran (THF) to give an aldehyde IVb[10,11] in 83% yield. Deoxygenation of IVb was accomplished by sodium borohydride reduction followed by removal of the produced allylic hydroxyl group (sulphur trioxide-pyridine, then lithium aluminium hydride in refluxing THF, overnight)[12] to afford VII[13] (78% yield). Regeneration of the hydroxyl group[7c] and subsequent route[7a] to the target molecule are already established.



VII



JH-II



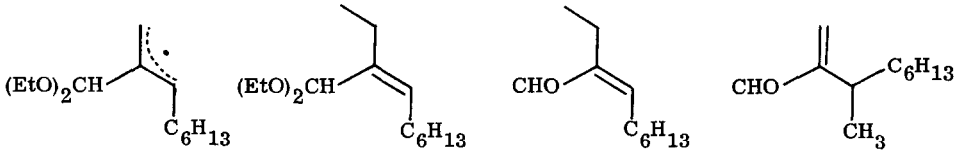
β-sinensal (VIc)

Under appropriate conditions the aldehyde Va[14] derived from IIIa (5% aq sulphuric acid-THF 1:1, r.t., 1.3 hr, quantitative yield) is transformed into (E)α,β-unsaturated aldehyde VIa by the formal S_N2' type introduction of hydride and elimination of acetoxyl group. When Va was mixed with 0.5 mol of sodium cyanoborohydride in methanol-acetic acid 10:1 at 0°, saturation of the olefinic bond occurred preferentially to afford the aldehyde VIa[15] in 61% yield. The reduction is much more efficiently performed by means of iron pentacarbonyl and 1,4-diazabicyclo[2.2.2]octane (DABCO) in wet dimethylformamide (DMF) (96% yield).[16] It should be noted that the incipient 1,1-disubstituted ethylenic linkage is reduced to produce a new, triply substituted one which remains intact under the conditions. The applicability of the methodology is demonstrated in the synthesis of β-sinensal (VIc), an important constituent of the odor and taste of Chinese orange oil (Citrus sinensus L.).[17] Reaction of a triene aldehyde IIc[17b,18] with 1.7 mol of the carbenoid I at -95° in THF yielded an adduct which was subsequently heated in ethanol in the presence of 5 mol of potassium carbonate for 2 hr, and the resulting alcohol was acetylated to give the acetal acetate IIIc[19] in 83% yield. Deprotection of the aldehyde group

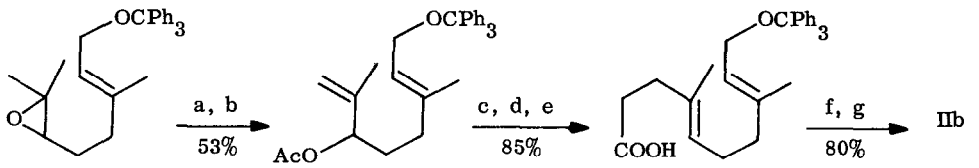
under the previous conditions (5% aq sulphuric acid-THF) resulted in polymerization of the large part of the product due to acid-sensitive 1,3-diene moiety. However, employing the recently reported procedure[20] we could effect the hydrolysis (silica gel-10% aq oxalic acid (10:1) suspended in dichloromethane, r.t., 1 hr) and obtained the aldehyde Vc[21] in 87% isolated yield. Reductive removal of the acetoxyl group was selectively attained with iron pentacarbonyl-DABCO in wet DMF (r.t., 1 hr), and β-sinensal (VIc) was produced in 95% yield. All the spectral data were consistent with those recorded.[17,22]

REFERENCES AND FOOTNOTES

1. T. Hiyama, A. Kanakura, H. Yamamoto, and H. Nozaki, Tetrahedron Lett., 0000 (1978)
2. Bp 110-116° (bath temp)/0.5 Torr.
3. The compound was characterized spectrometrically and analytically.
4. R. J. Anderson, C. A. Henrick, and J. B. Siddall, J. Am. Chem. Soc., 92, 735 (1970)
5. Bp 100-105° (bath temp)/17 Torr. NMR (CCl_4): δ 6.26 (t, J = 7.6 Hz, 1H), 9.28 (s, 1H); IR (neat): 2730, 1685, 1640, 1080, 792 cm^{-1}.
6. The cuprate reaction is explained (ref 4) to proceed through one-electron transfer yielding an allyl radical i of thermodynamically favourable W form. Subsequent methyl transfer, therefore, should give (Z) olefin ii and hence iii. In fact iii [NMR (CCl_4): δ 6.30 (t, J = 8 Hz, 1H), 10.06 (s, 1H)] was the major product when deacetalization was performed carefully, but isomerization to IVa occurred rapidly and completely upon purification on silica gel. Formation of an S_N2 type product iv was less than 5%.



7. (a) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, J. Am. Chem. Soc., 90, 5618 (1968). (b) E. J. Corey and H. Yamamoto, ibid., 92, 6637 (1970). (c) S. Tanaka, H. Yamamoto, H. Nozaki, K. B. Sharpless, R. C. Michaelson, and J. D. Cutting, ibid., 96, 5254 (1974)
8. The aldehyde was prepared as follows:



a: $LiNEt_2$; b: Ac_2O-Py; c: LiN(iPr)cC_6H_{11}, $tBuMe_2SiCl$; d: heat (70°); e: AcOH; f: $LiAlH_4$
g: $PyHClCrO_3$ Cf. J. A. Katzenellenbogen and K. J. Christy, J. Org. Chem., 39, 3315 (1974)

9. NMR (CCl_4): δ 1.17 (t, J = 7.2 Hz, 6H), 1.46 (s, 3H), 1.60 (s, 3H), 1.5-2.1 (m + s (δ 1.93), 11H), 3.2-3.6 (m, 6H), 4.78 (s, 1H), 5.0-5.5 (m, 5H), 7.0-7.5 (m, 15H); IR (neat): 1740 cm^{-1}.

10. NMR (CCl_4): δ 0.92 (t, J = 7.5 Hz, 3H), 1.47 (s, 3H), 1.63 (s, 3H), 2.0-2.5 (m, 10H), 3.52 (d, J = 7.2 Hz, 2H), 5.0-5.2 (m, 1H), 5.37 (t, J = 7.0 Hz, 1H), 6.22 (t, J = 7.2 Hz, 1H), 7.0-7.5 (m, 15H), 9.23 (s, 1H); IR (neat): 2740, 1688, 1644 cm^{-1}.

11. The concomitant (Z) isomer [NMR (CCl_4): δ 10.00] was quantitatively converted into the (E) isomer (IVb) by treatment with potassium carbonate in methanol (40°, overnight).

12. E. J. Corey and K. Achiwa, J. Org. Chem., 34, 3667 (1969)

13. NMR (CCl_4): δ 0.94 (t, J = 7.5 Hz, 3H), 1.48 (s, 3H), 1.61 (s, 3H), 1.64 (s, 3H), 1.7-2.1 (m, 10H), 3.52 (d, J = 6.0 Hz, 2H), 4.9-5.1 (m, 2H), 5.39 (t, J = 6.0 Hz, 1H), 7.0-7.5 (m, 15H).

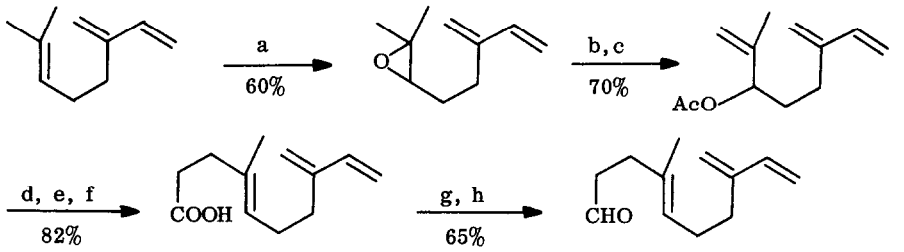
14. NMR (CCl_4): δ 0.7-1.8 (m, 13H), 2.00 (s, 3H), 5.47 (t, 1H), 5.98 (s, 1H), 6.25 (s, 1H), 9.48 (s, 1H).

15. NMR (CCl_4): δ 0.7-1.1 (t, 3H), 1.1-1.7 (m, 8H), 1.71 (s, 3H), 2.32 (q, J = 7.0 Hz, 2H), 6.34 (t, J = 7.5 Hz, 1H), 9.31 (s, 1H); IR (neat): 2730, 1688, 1641 cm^{-1}.

16. R. Noyori, I. Umeda, and T. Ishigami, J. Org. Chem., 37, 1542 (1972)

17. (a) A. F. Thomas, Chem. Commun., 947 (1967); J. Am. Chem. Soc., 91, 3281 (1969). (b) G. Büchi and H. Wüest, Helv. Chim. Acta, 50, 2440 (1967). (c) E. Bertele and P. Schudel, ibid., 50, 2445 (1967). (d) M. Baumann, W. Hoffmann, H. Pommer, Liebigs Ann. Chem., 1976, 1626. (e) α-sinensal synthesis: G. Büchi and H. Wüest, J. Am. Chem. Soc., 96, 7573 (1974)

18. The aldehyde was alternatively prepared according to the following scheme.



a: m-chloroperbenzoic acid; b: $LiN(iPr)_2$; c: Ac_2O-Py; d: $LiN(iPr)_2$, $tBuMe_2SiCl$; e: heat (70°); f: $PhCH_2\overset{+}{N}Me_3F^-$-aq MeOH; g: $LiAlH_4$; h: $PyHClCrO_3$

19. NMR (CCl_4): δ 1.18 (t, J = 7.4 Hz, 6H), 1.60 (s, 3H), 1.7-2.2 (m + s (δ 1.99), 11H), 3.46 (m, 4H), 4.8-5.3 (m, 9H), 6.27 (dd, J = 11, 17 Hz, 1H); IR (neat): 1740, 1595, 1230, 1115, 1050, 890 cm^{-1}.

20. F. Huet, A. Lechevallier, M. Pellet, and J. M. Conia, Synthesis, 63 (1978)

21. NMR (CCl_4): δ 1.60 (s, 3H), 1.7-2.3 (m + s (δ 2.03), 11H), 4.9-5.3 (m, 8H), 5.3-5.6 (m, 1H), 5.97 (s, 1H), 6.1-6.5 (dd + s (δ 6.24), 2H), 9.50 (s, 1H); IR (neat): 3080, 2700, 1740, 1690, 1595, 1355, 1220, 895 cm^{-1}.

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