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FURANOSESQUITERPENOIDS
ABSOLUTE CONFIGURATION OF PALLESCENSIN-1, -2, AND -A

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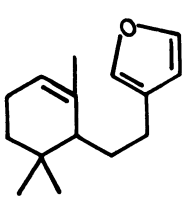
The chirality of asymmetric centers of pallescensin-1 (1a), -2 (2a), and -A (4a) was respectively assigned to be (R), (R), and (5S,10S) by the syntheses of 1a and 4a starting from (R)-(-)-α-cyclocitral (5a).

Recently, numerous furanosesquiterpenes, e. g., pallescensin-1 (1), -2 (2), -3 (3), and -A (4), were isolated from marine sponge Disidea pallescens by Cimino et al.[1] The structural assignments of these natural compounds are mainly based on spectral analyses, biosynthetic considerations and interrelation between them. However, since their absolute configurations have not yet been reported, the present authors attempted the total syntheses of the natural compounds in order to confirm the proposed structures and to elucidate the chirality of asymmetric centers. In this communication we wish to report the syntheses of pallescensin-1 and -A starting from (R)-(-)-α-cyclocitral (5a),[2] $[\alpha]_D$ - 610° (EtOH), and the absolute configurations of pallescensin-1, -2, -3, and -A.



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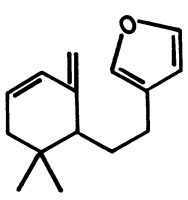

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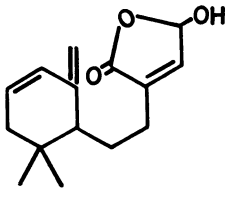

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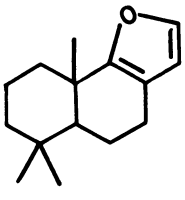
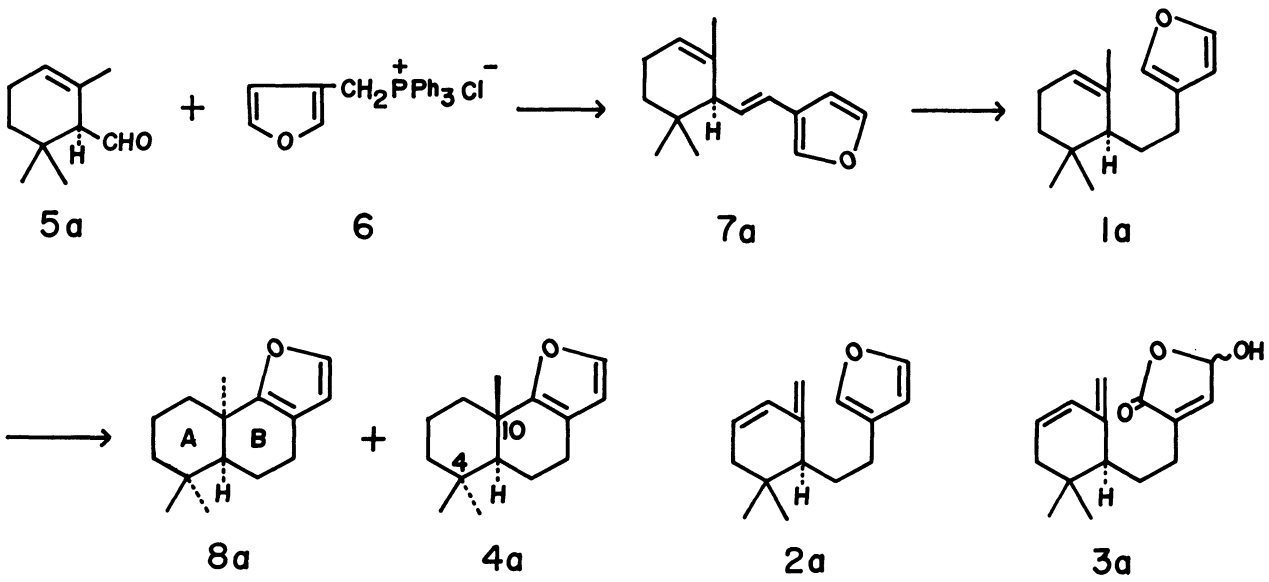


4

For the present synthesis 3-furylmethyltriphenylphosphonium chloride (6), mp



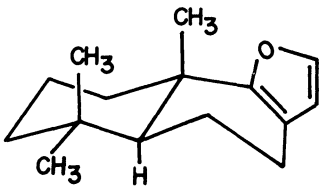
5a 6 7a 1a

8a 4a 2a 3a

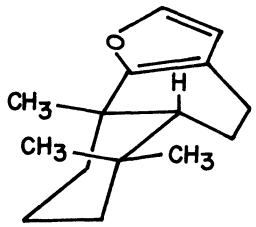
283-287°C dec., was prepared from 3-chloromethylfuran[3] and triphenylphosphine in benzene. The Wittig reaction of 5a with 6 in the presence of butyllithium was carried out in refluxing benzene for 3 h under nitrogen atmosphere and the resulting crude product was purified by column chromatography[4] on silica gel to afford a 3-vinylfuran derivative (7a: 70%), $[\alpha]_D$ - 272° ($CHCl_3$), NMR (CCl_4): 0.87 and 0.92 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.60 (3H, bs, $=\overset{|}{C}CH_3$), 5.40 (1H, m, $-CH=\overset{|}{C}-$), 5.63 (1H, dd, J=8 and 15 Hz, $-\overset{|}{C}H-CH=CH-$), 6.16 (1H, d, J=15 Hz, -CH=CH-), 6.40 (1H) and 7.28 (2H) (each bs, furan protons). In the NMR spectrum of 7a the vicinal coupling constant (J=15 Hz) of vinyl protons suggested the presence of a trans disubstituted double bond. The ethanol solution of 7a was then submitted to partial catalytic-hydrogenation over 5% Pd-C at r. t. for 40 min to give the corresponding dihydro derivative (1a: 79%), $[\alpha]_D$ - 89.5° ($CHCl_3$), whose NMR spectrum was identical with that of natural pallescensin-1. 1a: NMR (CCl_4), 0.88 and 0.96 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.68 (3H, bs, $=\overset{|}{C}CH_3$), 5.28 (1H, m, -CH=), 6.17, 7.13, and 7.26 (each 1H and bs, furan protons). Intramolecular cyclization of 1a with anhydrous aluminium chloride in dichloromethane was carried out at - 5°C for 15 min, and the crude product was purified by column chromatography[4] on silica gel to give 8a (20%), $[\alpha]_D$ - 27.0° ($CHCl_3$), and 4a (10%), $[\alpha]_D$ + 26.4° ($CHCl_3$) which was shown to be identical with natural pallescensin-A[5] by spectral comparison. 8a: NMR (CCl_4), 0.84 and 1.07 (each 3H and s, $-\overset{|}{C}(CH_3)_2$), 1.30 (3H, s, $C_{10}-CH_3$), 6.00 and 7.12 (each 1H, d, and J=2 Hz, furan protons). 4a: NMR (CCl_4), 0.93 and 0.94 (each 3H and s, $-\overset{|}{C}(CH_3)_2$),

1.18 (3H, s, C_{10}-CH_3), 5.97 and 7.06 (each 1H, d, and J=2 Hz, furan protons). The NMR spectra of 4a showed almost equivalent signals at δ 0.93 and 0.94 ppm due to the gem-dimethyl at the C-4 position, while that of 8a showed two non-equivalent ones at δ 0.84 and 1.07 ppm. It is well known[6] that the NMR spectra of the ring C aromatic tricyclic diterpenes possessing a trans A/B ring junction show signals at δ 0.91-0.98 ppm often in form of a six-proton singlet due to the C-4 gem-dimethyl and at δ 1.14-1.20 ppm due to the C-10 angular methyl. The close similarity of the NMR spectra of 4a and the trans tricyclic diterpenes suggested that the stereochemistry of the A/B ring junction in 4a and 8a was trans- and cis-configurations respectively. Thus, the absolute configurations of pallescensin-A (4a) and its cis-isomer (8a) could be assigned to be (5S,10S) and (5S,10R) respectively. The correlation of pallescensin-2 and -3 to pallescensin-A (4a) via pallescensin-1 was achieved by Cimino et al.[1] However, since there is no report on the specific rotation of natural and derived pallescensin-1, the stereochemical identity of the synthetic 1a and the natural compound could not be confirmed. Nevertheless, the co-occurrence and biosynthetic consideration[1] of pallescensin-A (4a) suggested that the absolute configurations of natural pallescensin-1, -2, and -3 except that of the butenolide moiety, are the same (R)-configuration as shown in 1a, 2a, and 3a, respectively.

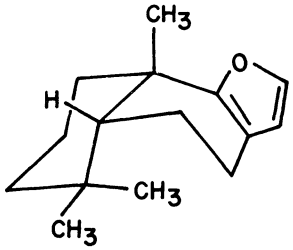
For comparison, the enantiomers of 1a and pallescensin-A were also synthesized by the same procedure starting from (S)-(+)-α-cyclocitral (5b), $[\alpha]_D$ + 580° (EtOH). Condensation of 5b with 6 gave the corresponding 3-vinylfuran derivative (7b: 78%), $[\alpha]_D$ + 266° ($CHCl_3$), which was then converted into a dihydro derivative (1b: 80%), $[\alpha]_D$ + 82.0° ($CHCl_3$). Intramolecular cyclization of 1b with anhydrous aluminium chloride gave cis- (8b: 22%), $[\alpha]_D$ + 21.5° ($CHCl_3$), and trans-compound (4b: 13%), $[\alpha]_D$ - 22.8° ($CHCl_3$). The NMR spectrum of the trans-compound (4a or 4b) showed a singlet signal due to an angular methyl group at δ 1.18 ppm, while the cis-isomer (8a or 8b) showed a moderately deshielded angular methyl singlet at δ 1.30 ppm. This indicates that the angular methyl group in both isomers has the different spatial relationship to the furan ring and that the cis-isomer exists in a non-steroidal conformation (8b'), because the corresponding steroidal conformation (8c) would have the angular methyl and the furan ring in nearly the same spatial relationship as in the trans-isomer (4a') and consequently the angular methyl signal would be expected to be nearly at the same frequency as that of the trans-isomer.



4a'



8b'



8c

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1) G. Cimino, S. De Stefano, A. Guerriero, and L. Minale, Tetrahedron Lett., 1975, 1417, 1425.

2) C. H. Eugster, R. Buchecker, Ch. Tsharner, G. Uhde, and G. Ohloff, Helv. Chim. Acta, 52, 1729 (1969).

3) E. Sherman and E. D. Amstutz, J. Am. Chem. Soc., 72, 2195 (1950).

4) Hexane was used as the eluent.

5) The reported specific rotation of natural pallescensin-A is + 9.7°.[1)]

6) C. H. Brieskorn, A. Fuchs, J. B. Bredenberg, J. D. McChesney, and E. Wenkert, J. Org. Chem., 29, 2293 (1964).

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