HETEROCYCLES, Vol. 19, No 3, 1982

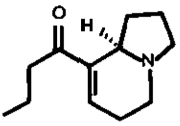
ALTERNATIVE TOTAL SYNTHESIS OF ELAEOCARPUS ALKALOIDS†

Hirotaka Otomasu, Noriyuki Takatsu, Toshio Honda, and Tetsuji Kametani†
Hoshi College of Pharmacy, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

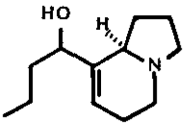
Abstract——An alternative synthesis of Elaeocarpus alkaloids using 1,3-dipolar cycloaddition of Δ^1-pyrrolin-1-oxide with the enone to give the isoxazolidine as a key intermediate is described.

Recently we have published[1-3] the stereoselective synthesis of carbapenem antibiotics, thienamycin and its derivatives, by the application of 1,3-dipolar cycloaddition of nitrile oxides with crotonic ester as a key reaction. As an extension of our work on this cycloaddition reaction, we have investigated an alternative synthesis of Elaeocarpus alkaloids, such as elaeokanine A (1), B (2), and C (3), isolated by Johns et al.[4] from the leaves of Elaeocarpus species. These alkaloids are known to possess a characteristic trans-indolizidine ring system, and several synthetic methods for them have been reported[5-12] to date. Our synthesis of Elaeocarpus alkaloids began with the preparation of an isoxazolidine as a key intermediate which was obtained by 1,3-dipolar cycloaddition of a nitrone with an enone.[13]

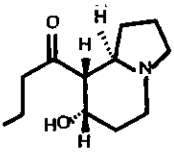
Thus, the requisite enone (8) was prepared as follows. 3-Butyn-1-ol (4) was converted into its tetrahydropyranyl ether (THP) (5), whose alkylation with n-butyraldehyde in the presence of n-butyllithium afforded the acetylenic alcohol (6) in 82% yield from 4. Reduction of (6) with lithium aluminium hydride in tetrahydrofuran gave rise to trans-olefin (7), which was then oxidised with manganese dioxide to



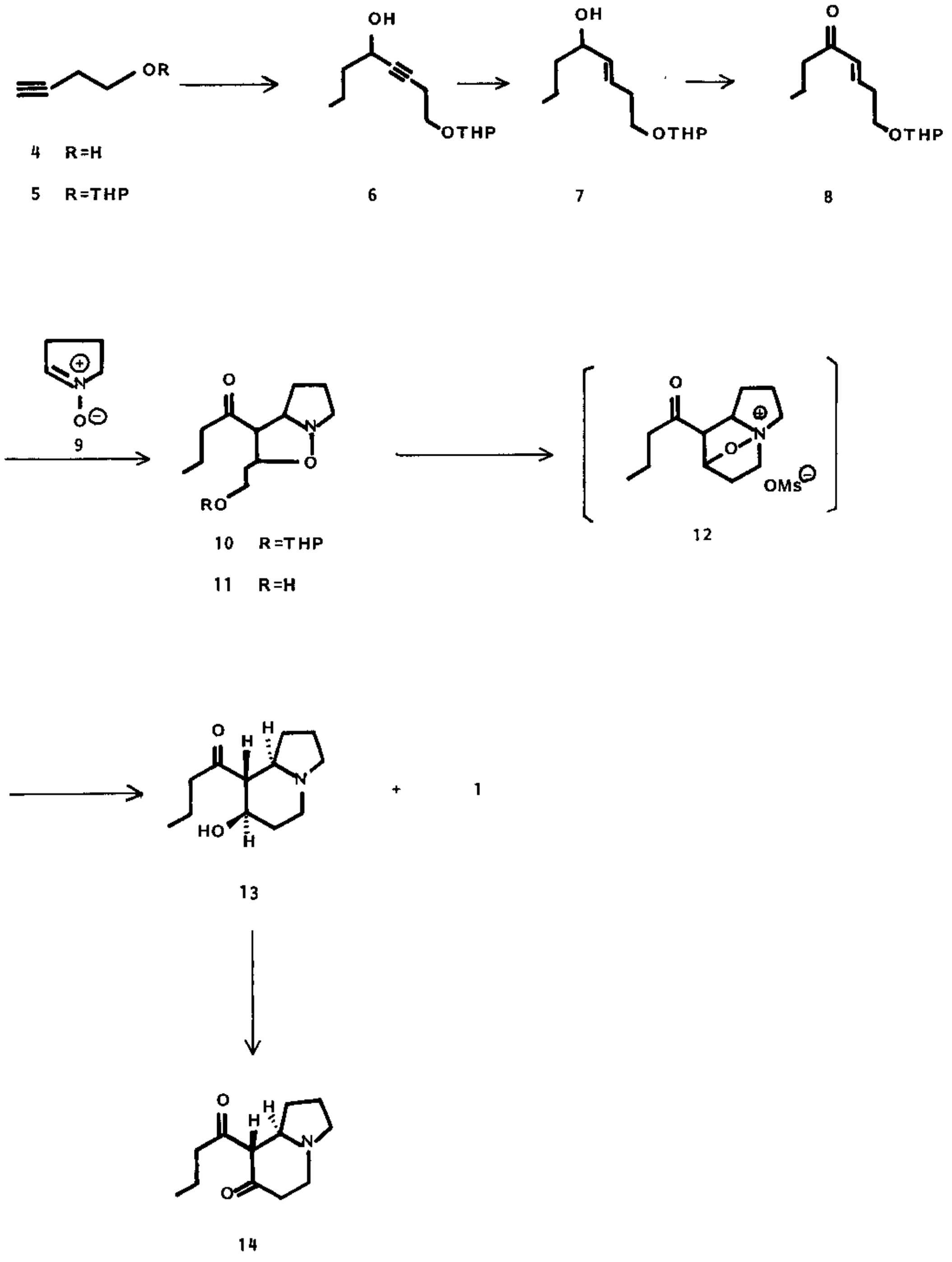
1



2



3


OR
4 R=H
5 R=THP
OH
OTHP
6
OH
OTHP
7
O
OTHP
8
9
O
N
O
RO
10 R=THP
11 R=H
O
O
N
OMs
12
O
H
H
N
HO
H
13
+ 1
O
H
H
N
O
14

furnish the trans-enone (8) in 50 % yield from (6). 1,3-Dipolar cycloaddition of (8) with Δ^1-pyrrolin-1-oxide (9) was carried out in refluxing chloroform to yield the stereoisomeric mixtures of adducts (10) in 88 % yield. After the deprotection of tetrahydropyranyl ether of (10) with 10 % aqueous hydrochloric acid in tetrahydrofuran, the resulting primary alcohol (11) was converted to quaternary salts (12) by mesylation, which without purification was treated with zinc powder in 50 % aqueous acetic acid to afford the β-hydroxy ketone (13) as a major product[14] in 26 % yield from (10). The stereochemical assignment was deduced from its spectral data[15] and the formation of (13) suggested that the epimerisation at the C_4-position of (11) occurred during its conversion into (13).
Finally the β-hydroxy ketone (13) was oxidised to the diketone (14)[16] whose structure was unambiguously supported by its spectral data[4,10]. Since the convertion of (14) to elaeokanine C has already been reported[4], this synthesis constitutes a formal synthesis of elaeokanine C.
Furthermore, 1,3-dipolar cycloaddition of the cis-enone with Δ^1-pyrrolin-1-oxide is under investigation.

ACKNOWLEDGEMENTS

The authors are greateful to Miss A. Matsunaga and Miss H. Furuyama, Hoshi College of Pharmacy, for manuscript preparation.

REFERENCES

1 T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, J. Am. Chem. Soc., 1980, 102, 2060.

2 T. Kametani, S.-P. Huang, T. Nagahara, and M. Ihara, J. Chem. Soc. Perkin I, 1981, 2282.

3 T. Kametani, A. Nakayama, Y. Nakayama, T. Ikuta, R. Kubo, E. Goto, T. Honda, and K. Fukumoto, Heterocycles, 1981, 16, 53.

4 N. K. Hart, S. R. Johns, and J. A. Lamberton, Austral. J. Chem., 1972, 25, 817.

5 F. Lions and A. M. Willison, J. Proc. Roy. Soc. N. S. Wales, 1940, 73, 240.

6 N. J. Leonard, S. Swann, Jr., and J. Figueras, Jr., J. Am. Chem. Soc., 1952, 74, 4620.

7 A. H. Beekett, R. G. Lingard, and A. E. E. Theobald, J. Med. Chem., 1969, 12, 563.

8 J. J. Tufariello and Sk. A. Ali., Tetrahedron Letters, 1979, 4445; this paper has provided the efficient route to the synthesis of elaeokanine alkaloids using 1,3-dipolar cycloaddition of a nitrone with an olefin.

9 A. S. Howard, G. C. Gerrans, and C. A. Meerholz, ibid., 1980, 21, 1373.

10 T. Watanabe, Y. Nakashita, S. Katayama, and M. Yamauchi, Heterocycles, 1980, 14, 1433.

11 H. F. Schmitthenner and S. M. Weinreb, J. Org. Chem., 1980, 45, 3373.

12 B. P. Wijnberg and W. N. Speckamp, Tetrahedron Letters, 1981, 22, 5079.

13 J. J. Tufariello, Acc. Chem. Res., 1979, 396 and references cited therein.

14 Elaeokanine A was also obtained as a minor product in ca. 5 % yield from (10), probably arising from elaeokanine C by dehydration.

15 IR $\nu_{max}(CHCl_3)$: 1705 cm^{-1} : NMR $(CDCl_3)$ 0.90(3H, t, J = 7 Hz, 13-Me), 1.60 (2H, tq, J = 7 and 7 Hz, 12-CH_2), 2.54 (2H, t, J = 7 Hz, 11-CH_2), 2.25 (1H, dd, J = 10 and 10 Hz, 8-H), 3.87 (1H, dt, J = 5 and 10 Hz, 7-H): MS m/e 211(M^+).

16 IR$\nu_{max}(CHCl_3)$ 1720 - 1690 cm^{-1} (broad) [lit[10]., 1720 - 1680 cm^{-1}] : MS m/e 209 (M^+), 208, 190, 181, 166, 164, 152, 139, 138 (base peak), 136, 120.

† This forms "Studies on the Syntheses of Heterocyclic and Natural Compounds." Part 970.

Received, 7th December, 1981