STUDIES ON THE SYNTHESIS OF MORPHINAN AND ITS RELATED COMPOUNDS[1]: NEW ENTRY TO THE CONSTRUCTION OF BENZOMORPHAN RING SKELETON

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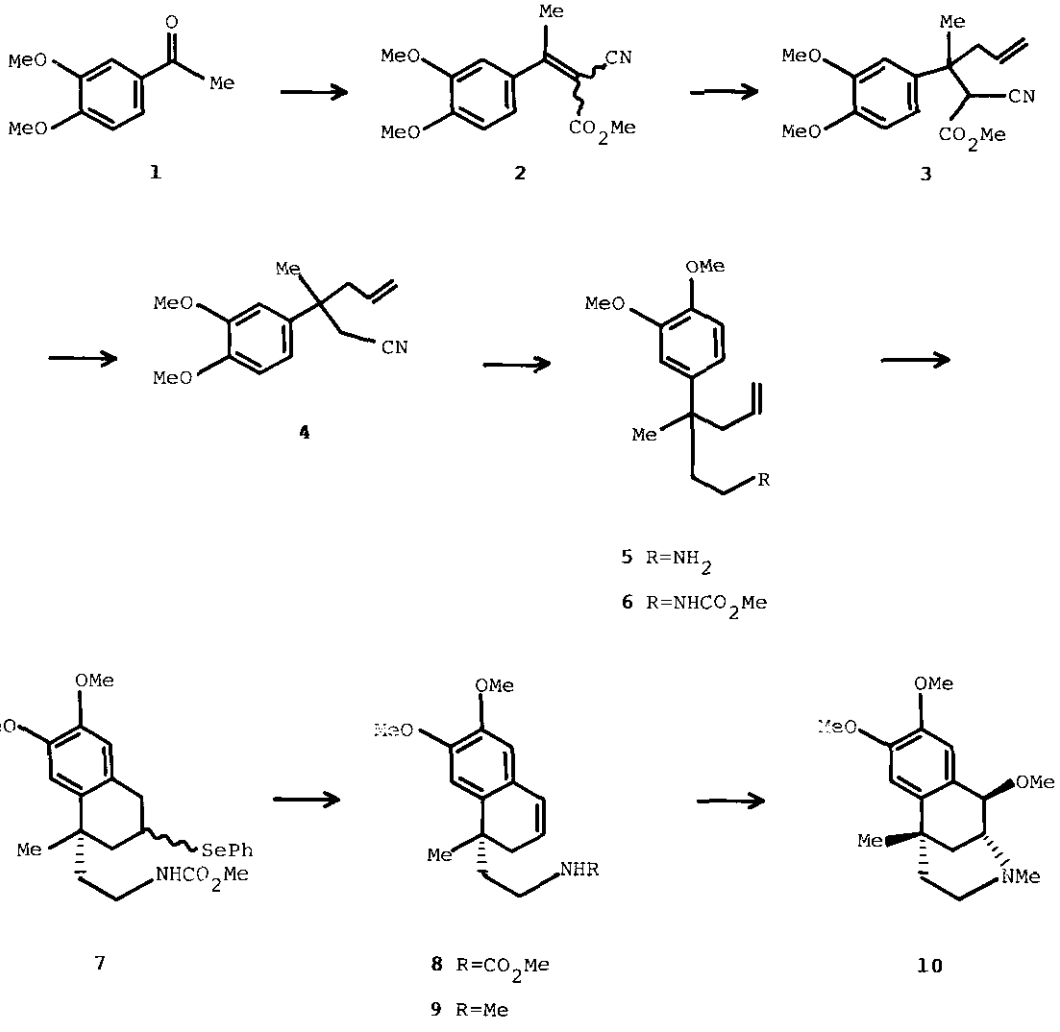
Abstract ——— Construction of a benzomorphan ring system was achieved by employing phenylselenenyl chloride mediated arene-alkene cyclization and subsequent C-ring formation via an amilynium ion intermediate, as key steps.

Benzomorphans have been known to be analgesic agents having no addiction liability,[2,3] and considerable effort has been devoted towards their syntheses.[4] In many of the syntheses of benzomorphan derivatives so far reported, the Grewe cyclization serves as the key reaction to construct the basic ring skeleton. Our interest in this field of chemistry grew out of a desire to find a new and general route for constructing morphinan and its related compounds.

We here report a novel synthesis of benzomorphan ring system, which involves arene-alkene cyclization mediated by phenylselenenyl group to prepare its A/B ring system and the silver catalyzed C-ring formation through an amilynium ion intermediate which was successfully utilized for the synthesis of a D-ring of morphinan derivatives in our previous work.[5]

Thus, the requisite starting material was prepared as follows. The acetophenone (**1**) was condensed with methyl cyanoacetate in the presence of benzylamine in benzene to give the cynnamic acid derivative (**2**) in 56% yield. 1,4-Addition of diallylcopper lithium to **2** in dry tetrahydrofuran afforded the ester (**3**), as an inseparable mixture of diastereomers whose hydrolysis with 1N ethanolic potassium hydroxide solution, followed by decarboxylation provided the cyanide (**4**) in 56% yield from **2**. Lithium aluminum hydride reduction of **4** gave the amine (**5**), which



was further converted to the corresponding urethane derivative (**6**) by treatment with methyl chloroformate and triethylamine in benzene. With the requisite starting material available, a study was made of the best condition for the arene-alkene cyclization to construct its A/B ring system. Although phenylselenenyl chloride mediated carbon-nitrogen bond forming reaction of urethane derivative with olefins was well-recognized,[6] we decided to adopt this procedure for the arene-alkene cyclization, because it would be expected that the presence of electron donating group on aromatic ring would accerelate the desired cyclization superior to the known carbon-nitrogen bond formation. Treatment of **6** with phenylselenenyl chloride in methylene chloride brought about the desired

cyclization to yield the functionalized tetralin derivative (**7**)[7] in 62% yield, as expected, together with the small amount of the C-N cyclized product. None of indane derivative was detected in this reaction, interestingly. Oxidative elimination of the phenylselenenyl group by treatment with sodium periodate in methanol-tetrahydrofuran-water (7:20:3 v/v) at ambient temperature afforded the olefin (**8**) as the sole product in 71% yield. Reduction of **8** with lithium aluminum hydride gave the amine (**9**), which was then treated with N-chlorosuccimide to yield the N-chloro compound. Finally the C-ring formation was carried out through the amilynium intermediate by treatment of the N-chloro derivative with silver oxide in methanol to afford the desired benzomorphan derivative (**10**) in 36% yield.

Thus, the construction of benzomorphan ring system was achieved by employing arene-alkene cyclization as the key reaction and this strategy would be applicable to the synthesis of naturally occurring morphinan alkaloids.

REFERENCES

1. Previous work in this series see: T. Kametani, Y. Suzuki, and T. Honda, Heterocycles, 1985, **23**, 563.
2. S. Archer, N. F. Albertson, L. S. Hauis, A. K. Pierson, and J. G. Bird, J. Med. Chem., 1964, **7**, 123.
3. N. F. Albertson and W. F. Wetterau, J. Med. Chem., 1970, **13**, 302.
4. T. Kametani, K. Kigasawa, M. Hiiragi, and N. Wagatsuma, Heterocycles, 1974, **2**, 79, and references cited therein.
5. T. Kametani, Y. Suzuki, and T. Honda, Heterocycles, 1985, **23**, 305.
6. D. L. J. Clive, V. Farina, A. Singh, C. K. Wong, W. A. Kiel, and S. M. Menchen, J. Org. Chem., 1980, **45**, 2120.
7. IR ($CHCl_3$) 3400, 1710, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (0.75H, s), 1.30 (2.25H, s), 3.63 (3H, s), 3.79 (3H, s), 3.83 (3H, s), 4.50 (1H, br s), 6.46 (1H, s), 6.71 (1H, s).
8. IR ($CHCl_3$) 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (3H, s), 2.54 (3H, s), 3.52 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 4.18 (1H, br s), 6.74 (1H, s), 6.81 (1H, s); MS m/z 291 (M^+). High MS Calcd for $C_{17}H_{25}NO_3$ m/z 291.1832. Found m/z 291.1804.

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