Satisfactory elemental analyses were obtained for new compounds 1b,c and 2a,b.

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Registry No. 1a, 111159-67-2; 1b, 111159-68-3; 1c, 111159-69-4; 1d, 111159-70-7; 1e, 111159-71-8; 3a, 111159-72-9; 3b, 111159-73-0; 5a, 111159-67-2; 5b, 111159-68-3; 6a, 111159-69-4; 6b, 111159-70-7; 6c, 111159-71-8; 6d, 111159-72-9; 6e, 111159-73-0.

Improved Synthesis of 3-Substituted 7-Methoxybenzofurans, Useful Intermediates for Preparation of Morphine Analogues

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Interest in the synthesis of morphine (1), codeine (2), and their analogues and their pharmacologic properties as useful analgesics continues unabated. Several syntheses and synthetic approaches have been described recently.

For a proposed route to analgesics of the morphine class, we required a good supply of 3-[2-(dimethylamino)ethyl]-7-methoxybenzofuran (3). Although this was an unknown compound, the analogous monomethyl amine 4 had been prepared by Ciganek and used in his synthesis of a morphine fragment. However, this preparation requires nine steps from commercially available o-vanillin (5), affords 3 via the ketone 6 in reproducible yields of only 10–12% in our hands, and was therefore for us not applicable to the large-scale laboratory preparation of 3. For this reason we have developed a rapid and efficient synthesis of 3 requiring only three operations from commercially available material.

2,3-Dimethoxybenzoic acid (7) was converted into the known acid chloride 8 in 95% yield by the standard method. Treatment of 8 with ethereal diazomethane followed by stirring the solution with glacial acetic acid at 25 °C afforded the ketone 6 in 64% yield. This reaction was described in 1956 by Richtzenhain and Alfredsson, but their somewhat vague experimental description gives no

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yield for the process.6 The reaction presumably proceeds via the acyl diazonium acetate 10, produced by protonation of the initially formed diazo ketone 9. Intramolecular displacement of nitrogen from 10 by the lone pair of the o-methoxy group would give the oxonium acetate 11, which would then lead to 6 by loss of methyl acetyl. By this route, the ketone 6 is available from the acid 7 in only two steps in 50% yield.

Conversion of 6 into the desired [dimethylamino]ethylbenzofuran 3 was accomplished in a one-pot reaction. Condensation of the known \([N,N\text{-dimethylcarbamoyl}]-\text{methylene} \text{triphenylphosphorane (12)}\)7 with 6 in refluxing toluene for 18 h followed by removal of the toluene, addition of THF, and treatment at 0 °C with lithium aluminum hydride gave, after aqueous workup, the desired amine 3 in 84% yield. Thus this potential intermediate for the synthesis of morphine analogues is available in three steps from 7 in an overall yield of 51% by a reaction sequence that may be amenable to scale-up.

Finally, it should be pointed out that Ciganek's intermediate 4 can also be prepared via this route by treatment of 3 with vinyl chlorofomate8,9 and hydrolysis of the resultant vinyl carbamate 13, in an overall yield of 70%.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer 710B spectrometer. 1H NMR spectra were recorded at

28.1097.

Notes

(6) For further studies on this reaction, see: Dallacker, F.; Forb, W. Jutaus Liebig Ann. Chem. 1986, 694, 98.

(7) This ylide was prepared by the method of Croce,8 but instead of using the crude product, we first recrystallized 12 from ether to afford crystals of much higher melting point (170 °C) than that reported (151 °C). Other examples of Wittig reactions of this type can be found in the work of Eliz and co-workers.9


(12) Duckling of peaks is due to the presence of two conformers about the N-CO bond of the carbamate.
The diterpene hydrocarbon laurenene (1), isolated in 1979 from *Dacrydium cupressinum* by Corbett and coworkers, is unique among natural products in being the only fenestrane known to occur in nature. The presence of several [4.4.4.5], [4.4.5.5], [5.5.5.5], and larger fenestranes is the methodology for the construction of the [5.5.5.7]-fenestrane ring system 2 present in it. While the synthesis of several [4.4.4.5], [4.4.5.5], [5.5.5.5], and larger fenestranes has been reported in recent years, the synthetic entry into the ring system 2 has not yet appeared in the literature. We describe here a novel approach that has led to the attainment of a derivative of laurenene.* While the synthesis of several [4.4.4.5], [4.4.5.5], [5.5.5.5], and larger fenestranes has been reported in recent years, the synthetic entry into the ring system 2 has not yet appeared in the literature. We describe here a novel approach that has led to the attainment of a derivative of laurenene.*

At the very outset, we recognized the carbocyclic ring system 2 as an angular triquinane (heavy lines) spanning a four-carbon bridge on the methylenes adjacent to the spirocenter. It was therefore tempting to adopt our general cationic transannulation approach 4 (Scheme I) to the angular triquinanes as the synthetic strategem for the construction of the fenestrane ring system 2. Consequently, generation of the bridged tricyclic cation 5 and its cyclization to 6 became our main concern.

![Scheme I](image)

Readily available allylclooctotetone 7 was selected as the starting point and regioselectively alkylated with 1,4-dibromobutane, under kinetically controlled conditions, to furnish the trans-dialkylated cyclooctotetone 8, Scheme I. The allyl group in 8 was transformed into an acetyl side chain through Wacker-type oxidation employing the Tsuji reaction conditions 6 to furnish the 1,4-diketone 9 in good yield. Internal aldo cyclization of 9 was achieved with sodium hydride under controlled conditions to deliver the bicyclic enone 10 as a single isomer. The structure of 10 was fully secured through its characteristic 13C NMR lines at δ 207.6, 187.2, and 126.0 due to a β,β-disubstituted cyclopentenone moiety. 4.7

The next step was crucial and required the four-carbon bridge formation through intramolecular bromide displacement from the α-position of the enone moiety in 10. This was realized through the dienolate generation with sodium hydride in refluxing toluene. A mixture of three tricyclic enones 11a,b and 12 (1:1) was obtained. The same mixture of three enones could be obtained directly from the diketone 9 on treatment with large excess of sodium hydride in boiling toluene. However, hydrogenolysis of the bromide in 9 was noticed as a competing reaction under these conditions. The three enones 11a,b and 12 could be separated through a combination of column chromatography and HPLC. The gross structure of 11a and 11b and their epimeric nature could be discerned from their spectral data. But, it was not possible to distinguish between them and, therefore, the epimeric mixture 11a,b was deployed for further reactions. The unwanted spiro enone 12 was readily identified on the basis of a quaternary sp3 carbon resonance at δ 54.3 (s) in the 13C NMR spectrum besides other complementary data. With the acquisition of the tricyclic enones 11a,b, attention was turned toward the key transannular cyclization step 5 → 6. The enone mixture was exposed to a variety of protic acids (CF3COOH, aqueous HClO4, CF3SO3H) and

![Diagram](image)