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Bilane Synthesis through Bilene-a: An Alternative Approach

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Abstract: An alternative approach to bilanes has been developed which involves reduction of a bilene-a derivative with an unprotected terminal α position. The required bilene-a was constructed by acid-catalyzed condensation of an appropriate tripyrrane carboxylic acid with a formylpyrrole. The new route is demonstrated by the syntheses of aminomethylbilane and 18-butyrate aminomethylbilane.

A bilane molecule consists of four pyrrole rings linked together by three methylene bridges at the α-pyrrolic positions. Interest in this type of compound stems mainly from research on porphyrin and vitamin B_{12} biosynthesis. [1]

During our studies of the mechanism of vitamin B_{12} biosynthesis, we were in need of an efficient procedure to synthesize bilanes. Two types of methods for bilane synthesis exist in the literature. The first is the direct preparation of the bilanes by coupling two dipyrromethane precursors bearing the desired array of substituents, while the second method involves reduction of bilenes or biladienes to the corresponding bilanes. Due to their array of π–electrons, most bilanes are very unstable toward oxygen and acids that bring about oxidation and intermolecular exchange of the pyrrole rings. Therefore, their handling requires exceptionally careful techniques. Mild conditions, which do not involve strong acids, have to be used in the synthesis of the pure isomers of unsymmetrically substituted bilanes. Another critical aspect of planning for bilane synthesis is the introduction of suitable protecting and stabilizing groups into the building blocks.

The use of a bilene-a in bilane synthesis was first reported (without experimental detail) by Franck and Rowold. [2] They prepared aminomethylbilane (AMB, 1, Scheme 1) by hydrogenation of a bilene-a whose terminal α position was protected by a benzyl ester group.

Now we wish to report an alternative approach to bilanes which involves reduction of a bilene-a derivative with an unprotected terminal α position.

Coupling reaction of the formylpyrromethane 2 with PBG lactam ester 3 catalyzed by hydrobromic acid gave the tripyrrene hydrobromide 4 in 92% yield (Scheme 1). Hydrogenolysis of tripyrrene 4 over palladium on charcoal cleaved the benzyl ester with concomitant reduction of the bridge double bond to give tripyrrane

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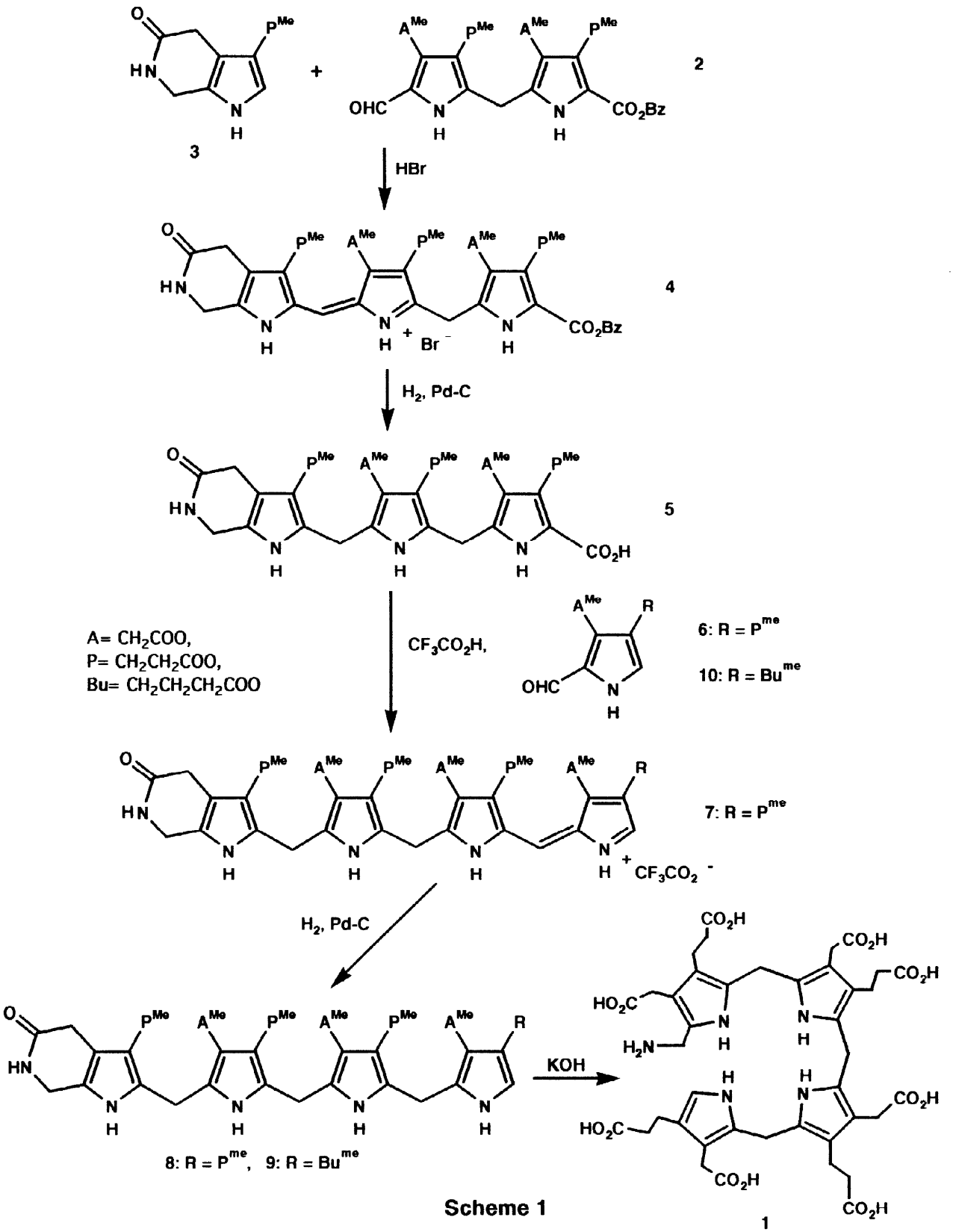
3
2
HBr
4
H_2, Pd-C
5
A= CH_2COO,
P= CH_2CH_2COO,
Bu= $CH_2CH_2CH_2COO$
CF_3CO_2H,
6: R = P^{me}
10: R = Bu^{me}
7: R = P^{me}
$CF_3CO_2^-$
H_2, Pd-C
8: R = P^{me}, 9: R = Bu^{me}
KOH
1

Scheme 1

acid 5. For elongation of the tripyrrane 5 to a tetrapyrrole, Franck and Rowold [2] employed an α-free tripyrrane which was derived from 5 by decarboxylation. The decarboxylation step was, however, low yielding (33%). Therefore, we decided to investigate the direct reaction of tripyrrane acid 5 with formylpyrrole 6. When 5 was treated with a 5% solution of trifluoroacetic acid in methanol and dichloromethane (1 : 1) at 4 ^{o}C overnight in the presence of 6, the reaction mixture showed an absorption at 485 nm indicative of a bilene-a chromophore. The crude product of bilene-a 7 was hydrogenated over 10% Pd-C in the presence of triethylamine to afford, after chromatographic separations, the pure AMB lactam 8. The overall yield of 8 was 17.5% starting from tripyrrene 4. Alkaline hydrolysis [3] of the lactam then yielded AMB 1.

In Franck's bilene-a route to AMB [2], the terminal α-free position (C-19) was protected by a benzyl ester. As can be expected, the removal of the benzyloxycarbonyl group during the late stages of bilane synthesis was problematic and thus is not a preferred procedure. For this reason, the α-free position of bilene-a 7 was not protected during our synthesis.

Following the newly developed method, 18-butyrate AMB lactam 9 was synthesized fron tripyrrane acid 5 and the butyrate pyrrole 10 [4] in an overall yield of 18% [5] (Scheme 1).

The method described above provides a general, alternative access to unstable bilane compounds.

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5. Procedure for making bilane 9: The tripyrrane acid 5 (freshly prepared by hydrogenation of 100 mg of the tripyrrene 4) was stirred with a solution of the formylpyrrole 10 (31 mg) in CH_2Cl_2 (10 mL) under nitrogen cooled on ice. A solution of trifluoroacetic acid (1 mL) in anhydrous MeOH (9 mL) was added. The solution was stirred on ice in the dark for 3h, then at room temperature for additional 3h. The resulted dark reddish solution had an UV maximum at 485 nm. The solution was evaporated *in vacuo* and residual trifluoroacetic acid was removed by co-distillation with benzene (2 X 60 mL) at room temperature. The solid residue was immediately suspended in 15 mL of anhydrous MeOH and 10 mL of $CHCl_3$, 10 drops of triethylamine was added and the color of the solution changed from dark red to dark green. The solution was hydrogenated over 90 mg of 10% Pd-C at 1 atm for 14 h, then filtered through Celite. The catalyst was washed with MeOH-CH_2Cl_2 (1 : 9 v/v; 30 mL) and the residue from combined filtrate was purified by TLC on 1 mm silica (6% MeOH and 0.05% triethylamine in CH_2Cl_2, Rf ~ 0.5). The product was washed with degassed MeOH and dried *in vacuo* to afford the aminomethylbilane lactam 9 (19 mg, 18.2% from the tripyrrene 4) as a brownish powder, mp 198-200^{o}C, green with Br_2 vapor. ^{1}H NMR: δ 1.83 (2H, quintet, J = 7.6 Hz, $CH_2\underline{CH_2}CH_2CO$), 2.33-2.50 (m) and 2.68-2.77 (m) (total 16H, 3 X CH_2CH_2CO and $\underline{CH_2}CH_2\underline{CH_2}CO$), 3.33, 3.43 and 3.44 (each 2H, s, 3 X CH_2CO), 3.36

(2H, br, CH_2CONH), 3.57, 3.59, 3.62, 3.64, 3.65, 3.66 and 3.70 (each 3H, s, 7 X OCH_3), 3.69, 3.73 and 3.75 (each 2H, s, 3 X CH_2-pyrrole), 4.40 (2H, br, CH_2NH), 5.98 (1H, br, CONH), 6.39 (1H, d, J = 1.9 Hz, pyrrole-H), 8.62 (1H, br), 9.07 (2H, br) and 9.23 (1H, br) (4 X NH). IR (KBr): υ_{max} 3330 (m), 2955 (m), 1731 (s), 1644 (m), 1437 (m), 1250 (m), 1171 (s) cm^{-1}. MS (FAB): m/e 947 (1.6%, M^+).