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1-AZA-SPIRO ANNELATION, II: A SYNTHETIC APPROACH TO 1-AZA-SPIRO[4.4]NONANES.

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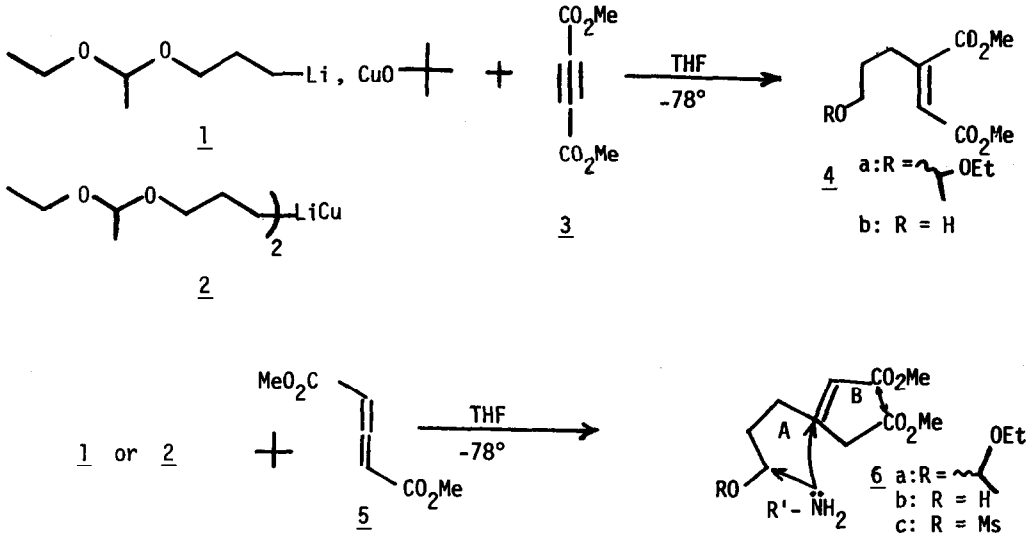
The 1-aza-spiro[4.4]nonane, -[4.5]decane[1] and -[5.5]undecane ring systems define some unique and synthetically challenging classes of alkaloids, the cephalotaxus[2] and histrionicotoxin[3] groups being of current interest to us. Reported herein are some preliminary findings concerning a formally very general method of producing functionalized 1-aza-spiro[4.4]-nonanes that should also readily afford the analogous decane and undecane systems.

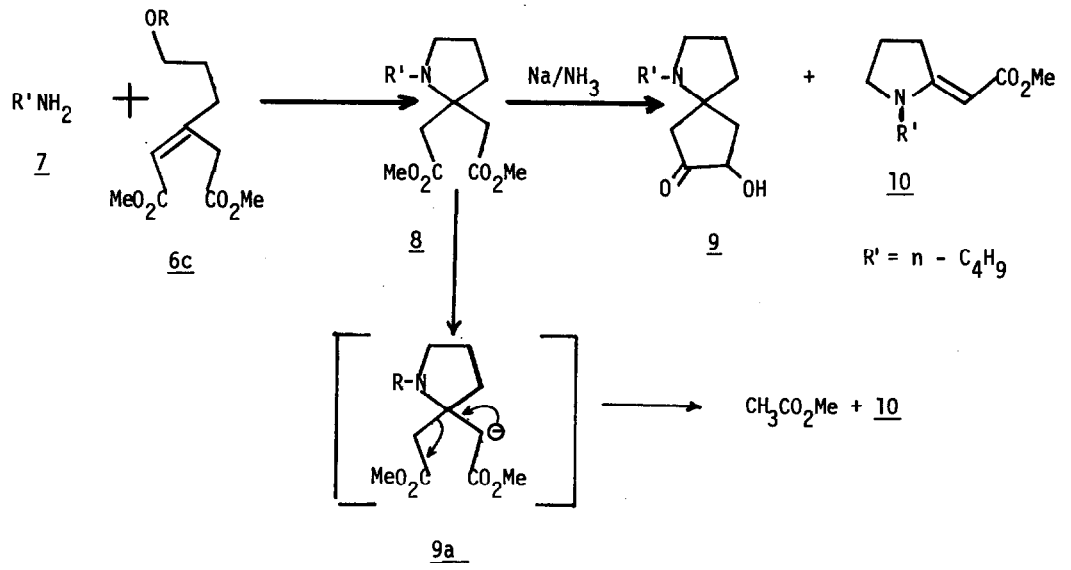
In earlier studies[4] related to insect chemistry we had investigated mixed cuprate (1) and dialkyl cuprate (2)[5] additions to acetylenes (3 to 4a, 75%)[6] and allenes (5 to 6a, 80%) which smoothly provided olefinic products with a variety of functional groups present.



Compound 6 could be envisioned as a 1-aza-spiro[4.4]nonane precursor through incorporation of nitrogen and a ring closure as illustrated above.

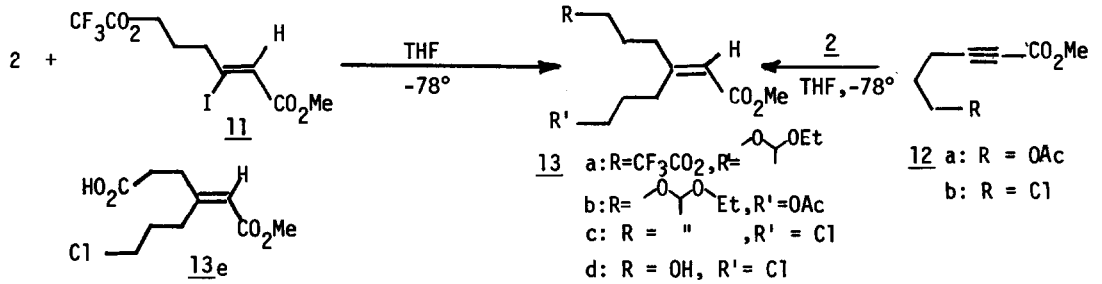
To prepare for nitrogen incorporation in 6, diester 6a was converted to alcohol 6b (10% aq. HCl/THF, 85%) and then mesylate 6c (CH_3SO_2Cl/pyridine, 95%). Aza-ring formation was then readily effected with 6c in refluxing dioxane by a concommitant alkylation and Michael addition of

primary amine 7, giving pyrrolidine 8 in good yield (67%). Spirane formation was completed via acyloin condensation to N-butyl-1-aza-8-hydroxyspiro[4.4]non-7-one, 9, (6- 15%) using



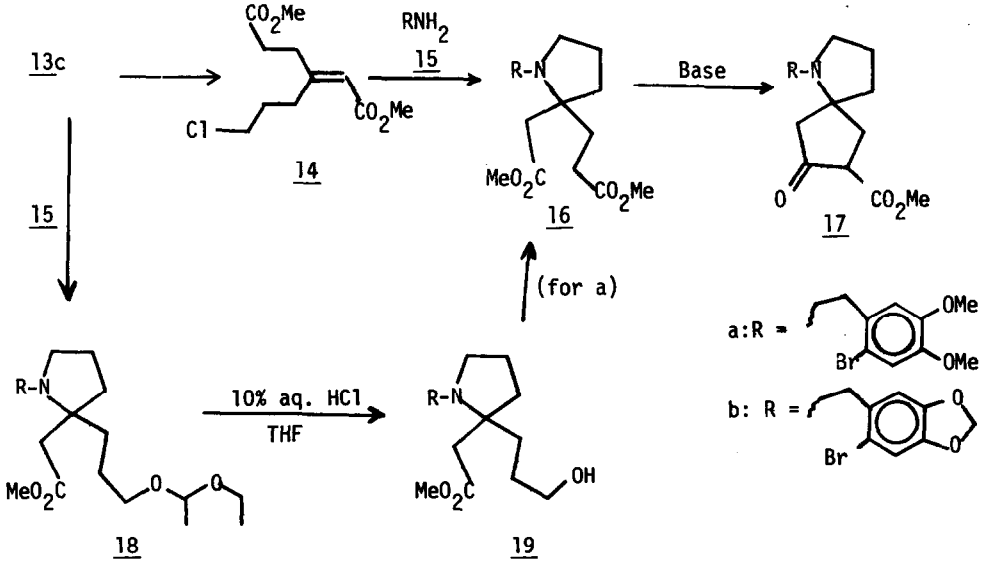
standard cyclization conditions.[7] In our hands the best yield of spirane 9 (15%) was achieved employing sodium in liquid ammonia. The major product isolated from these attempted reductive cyclization reactions was pyrrolidinylidine 10 which presumably arose from a retro-Michael-like process (9a → 10) as shown above.

To circumvent use of acyloin techniques we sought to homologate one of the carbomethoxyl units in 8 (i.e. compound 16) which would allow for eventual Dieckmann ring closure (16 → 17). Following the approach taken with allene 5 (vide supra), cuprate 2 was added to readily available allene equivalents 11 and 12 (a,b) providing 13a-c in good yield. Selective[8] functional group modification of 13 (a or b) could readily provide the homologue of 6c, suitable for formation of pyrrolidines 16.



It proved most convenient to convert chloride 13c to pyrrolidines 16 through the following sequence of reactions. Removal of the protecting group (13c → 13d, vide supra), oxidation to 13e (Jones/methyl ethyl ketone) and esterification ($CH_3OH/H^{\oplus}$) gave, without purification of the intermediate alcohol and acid, chlorodiester 14 in good overall yield (75% from 12b). Pyrrolidines 16 were then formed by treating 14 with primary amines 15 (a,b) in polar reaction media. The best yields (70-75%) of this simultaneous alkylation-Michael reaction were realized by heating under reflux in acetonitrile in the presence of sodium iodide (1 eq) and sodium carbonate (excess, anhydrous). Dieckmann condensation of these unsymmetrical pyrrolidines, 16, afforded N-alkyl-1-aza-8-carbomethoxyspiro[4.4]non-7-ones (17) as the major product; easily identified through the chemical shift of the methylene protons at position C6. Various bases could be employed to effect this conversion (sodium methoxide, sodium hydride, lithium diisopropylamide); lithium diisopropylamide (in THF) providing the best yields (86%, 17a and 72%, 17b).

Spirane precursor 16 was also available from an inverted sequence of reactions. Treatment of blocked chloride 13c with primary amines 15(a,b) gave pyrrolidines 18(a,b) in good yield (92 and 64%, respectively). Removal of the blocking group (18a → 19a, 71%; 18b → 19b, 83%), oxidation (Jones) and esterification of 19a (vide supra) gave the previously formed diester 16a. However, this latter preparation of 16a was not preferred due to reduced yields and a less convenient purification of this pyrrolidine diester.



The successful formation of 1-aza-spiro[4.4]nonanes in good yield using these general procedures would seem predictive of successful formation of the 1-aza-spiro[4.5]-decane and -[5.5]undecane systems through homologation of 2 and/or 12b. Studies testing these generalities are now underway.

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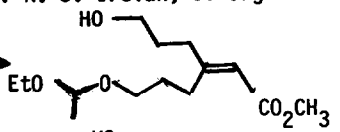
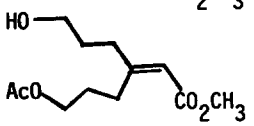
8. 13a → 

, 48% from 11.

13b → 

, 56% from 12a.