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Enantioselective synthesis of *trans*-fused bicyclo[5.3.0]decane systems via a tandem [4+3] cycloaddition-Nicholàs Reaction

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Abstract:

An enantioselective synthetic methodology to prepare *trans*-fused bicyclo[5.3.0]decane systems is presented. It is a very versatile methodology based on two key reactions: [4+3] cycloaddition reaction (to generate the seven-membered ring) and the Nicholas reaction (that facilitates the insertion of the five-membered ring). This methodology allows the easy preparation of a wide range of bioactive natural products containing the *trans*-fused bicyclo[5.3.0]decane system. The application of this methodology to the enantioselective synthetic approach to the pseudoguaiane carbon-skeleton is described.

Keywords: [4+3]-cycloaddition, Nicholas reaction, pseudoguaiane, enantioselective synthesis.

The design of synthetic methods to prepare efficiently polycyclic, multifunctional systems, in a stereoselective manner, is of great interest in synthetic chemistry. The 5,7-fused ring system is found in many natural products [1], most of them with interesting biological activity [2]. Our objective was to develop a strategy that would rapidly assemble the *trans*-fused bicyclo[5.3.0] ring system and be sufficiently versatile to allow further transformations and functionalisation within the rings and/or at the substituents.

Looking at surveys of strategies for the construction of the bicyclo-[5.3.0] carbon framework [3] it is possible to observe that the major strategy employed has been annulation of either the cyclopentane ring or the cycloheptane ring. In spite of the efforts reported to date, few of the methods give the *trans*-fused bicyclo[5.3.0]system [4] and fewer are enantioselective [5].

We have developed a synthetic methodology to construct *trans*-fused bicyclo[5.3.0]-decane carbon skeletons, conveniently functionalized and in an enantioselective manner. We report here the preliminary work of the application of this strategy to the enantioselective synthesis of a precursor of the sesquiterpene pseudoguaiane carbon-skeleton, which is the carbon framework of pseudoguaianolides, a large family of sesquiterpenic lactones with important antitumor activity [2]. It is a methodology based on two key reactions: [4+3] cycloaddition reaction [6] (to generate the seven-membered ring) and the Nicholas reaction [7] (that facilitates the construction of the five-membered ring, by electrophilic insertion of a propargyl

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C3-entity and further intramolecular cyclization). Moreover, it is a versatile synthetic strategy, as choosing a suitable substitution pattern in the propargyl, furan and haloketone precursors would allow preparation of a wide range of related structures.

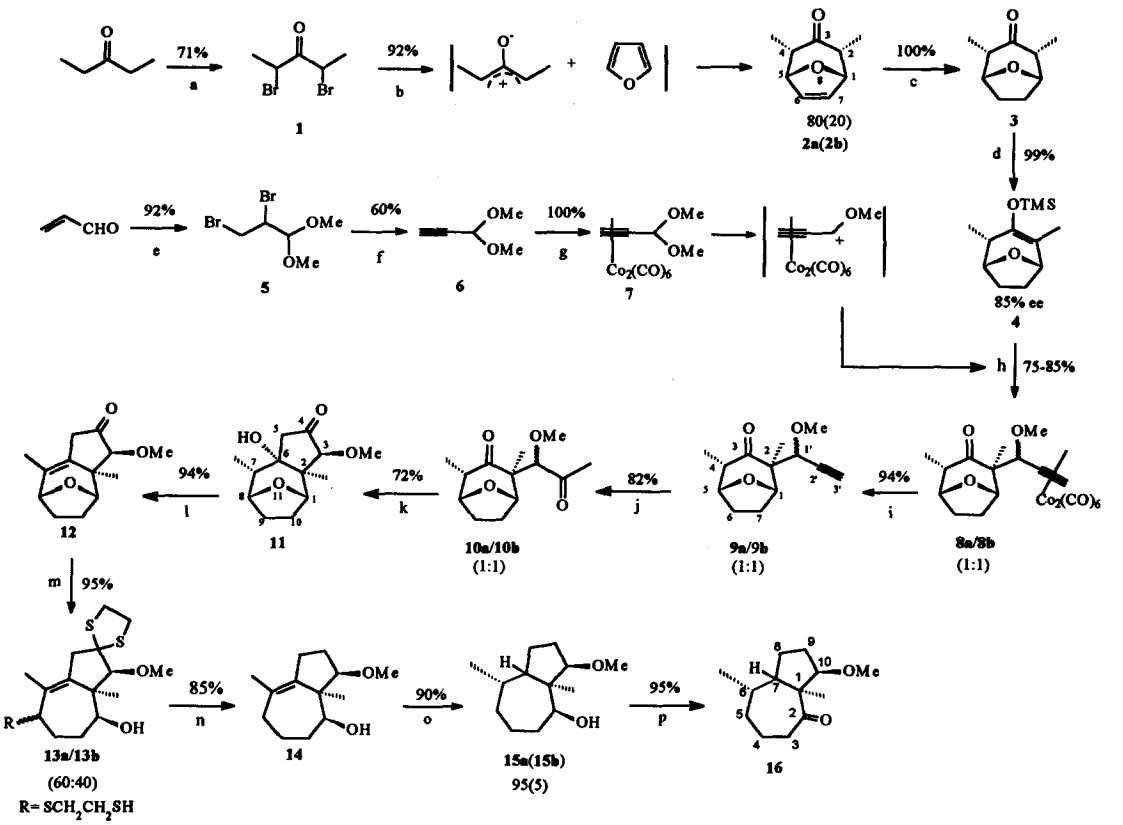
The cycloheptane moiety of our bicyclic system is prepared by a [4C(4π)+3C(2π)] cycloaddition reaction between furan and 1,3-dimethyl-2-oxyallyl cation (Scheme 1), generated *in situ* by reduction of 2,4-dibromo-3-pentanone **1** with Cu/NaI at 55°C [9]. This reaction afforded a mixture of diastereoisomers **2a/2b** in a 8:2 ratio and in 92% yield [8b-d] (Scheme 1). The major diastereoisomer **2a** has both methyl groups in a diequatorial configuration for a boat like conformation of the 1-oxan-4-one ring, and it is easily separable from **2b** by column chromatography. Haloketone **1** was obtained in 71% yield by bromination of cheap and commercially available 3-pentanone under acidic catalysis [8].

Catalytic hydrogenation of double bond C6-C7 afforded, in quantitative yield, oxabicyclic compound **3**. This optically inactive compound is efficiently converted into the enantio-enriched silyl enol ether **4**, in 99% yield and 85% ee, by its treatment at -78°C with the lithium (*S*, *S*)-1,1'-di(methylbenzyl)amide (Figure 1), in the presence of lithium chloride [9]. This chiral base is commercially available [10] in both enantiomeric forms but also could be efficiently prepared [11] by condensation of acetophenone with phenylethylamine followed by hydrogenation of the resulting imine.

This chirality induction is quite efficient because: a) it affords a good ee, whose improvement is under study in our laboratory; b) it is carried out in an early step in the synthetic pathway, which has an economical advantage; c) the chiral base can be recovered in a 95% yield (by extracting an ethereal solution of the crude reaction mixture containing it, with aq. (0.1M) HCl, at 0°C, without affecting the silyl enol ether **4**; e) the availability of both enantiomers of the chiral base allows the preparation of both enantiomers of the silyl enol ether.

The three-carbon subunit, necessary to assemble the five membered ring of the bicyclo [5.3.0] system, is introduced by an electrophilic attack of methoxypropargyl cation (stabilised as a dicobalt hexacarbonyl complex) on silyl enol ether **4** (Nicholas reaction). This propargyl cation is generated *in situ* from cobalt complex **7** by treatment with $BF_3.OEt_2$ [4a, 12]. Compound **7** is prepared in 55% overall yield starting from commercial acrolein[8a, 13] (see Scheme 1). The Nicholas propargylation of **4** produced in 75-85% yield (depending on work scale) a 1:1 diastereoisomeric mixture of **8a/8b**, epimers at C-1'. Due to the bulkiness of the organocobalt cluster, the attack of the propargylium cation is only possible on the *exo* face of silyl enol ether **4** forming only two diastereoisomers. The mixture of cobalt complexes **8a/8b** is demetallated with CAN/NEt_3 in acetone affording acetylenes **9a/9b** in 94% yield. Under these conditions both epimers are configurationally stable and the ratio **9a**:**9b** = 1:1 is identical to that of precursors. Hydration of the triple bond is carried out under neutral conditions by using mercury (II) *p*-toluenesulfamidate [4a-b, 14] to give diketones **10a/10b** (1:1) in 82% yield. Both diastereoisomers were separated by column chromatography, and single crystals of them were submitted to X-ray diffraction analysis to establish their relative configuration.

Aldol cyclization of methyl ketones **10a/10b** by using anhydrous KOH in absolute ethanol formed a single oxatricyclic compound **11** in 72% yield. It is worth noting that in this aldol reaction both epimers **10a/10b** give the same final product, probably via a keto-enol equilibrium. Circular dichroism studies were conducted on compound **11**, which allowed us to establish its absolute configuration (1*S*, 2*R*, 3*S*, 6*S*, 7*S*, 8*R*) as shown in Scheme 1.



a)Br_2 (2 equiv.), PBr_3 (cat.), 0°C; b) Furan, NaI, Cu, 55°C, chromatographic separation; c) H_2, Pd/C(10%), EtOH, r.t.; d) (*S,S*)-1,1'-dimethyldibenzylamine, BuLi, LiCl, -78°C, then TMSCl; e) Br_2, then $HC(OMe)_3$, MeOH; f) $[Bu_4N]OH$; g) $Co_2(CO)_8$, pentane, r.t.; h) $BF_3.OEt_2$, CH_2Cl_2, 0°C; i) CAN, Et_3N, acetone, 0°C; j) Hg(II) *p*-toluensulfamidate, EtOH/H_2O (85:15), reflux; k) Anh. KOH, abs. EtOH, r.t.; l) $SOCl_2$, Py, -24°C; m) $HSCH_2CH_2SH$, $BF_3.OEt_2$, 0°C; n) Raney-Ni, EtOH, reflux; o) H_2, Pd/C(10%), anh. MeOH, r.t., chromatographic separation; p) PCC, CH_2Cl_2, r.t.

Scheme 1.- *Synthetic pathway to prepare a trans-bicyclo[5.3.0] synthon, a precursor of the pseudoguaiane skeleton.*

Dehydration of **11** was performed by using $SOCl_2$/Py at low temperature affording compound **12** in 94% yield. Product **12** underwent two simultaneous transformations under treatment with ethanedithiol and $BF_3.Et_2O$ at 0°C (see Scheme 1): carbonyl protection as an ethanedithioketal and a concomitant regioselective oxygen-bridge cleavage to afford a 60:40 mixture of compounds **13a/13b** (epimers at the carbon bearing the mercaptoethylenethio group) in 95% yield.

Reduction of **13a/13b** with Raney-nickel in refluxing ethanol gave bicyclic compound **14**, as a single stereoisomer, in 85% yield. Hydrogenation of the tetrasubstituted double bond in **14** afforded diastereomeric products **15a/15b** (separable by CC). This reaction was accomplished with high yield (90%) and good stereoselectivity (95:5, *trans* : *cis*, respectively) by using

Pd/C(10%) as a catalyst in anhydrous MeOH at room temperature. Alcohol **15** was oxidised to ketone **16** in 95% yield by using PCC in CH_2Cl_2. Compound **16** is a versatile synthon having two functional groups that allow its further derivatization.

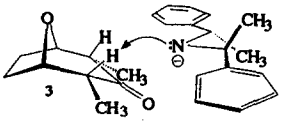


Figure 1.- Stereo-differentiation in the attack of lithium (S,S)-1,1'-di(methylbenzyl)amide .

We can conclude that we have developed a methodology to synthesise, in an enantioselective manner, functionalized *trans*-fused bicyclo[5.3.0]decanes, with induction of enantioselectivity at an early step of the synthetic pathway. We have exemplified this synthetic strategy for the preparation of a precursor of the sesquiterpene pseudoguaiane carbon framework. Other applications of this methodology to the synthesis of biologically active natural products are under development in our laboratory.

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