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Synthesis of an azaspirane via Birch reduction alkylation prompted by suggestions from a computer program

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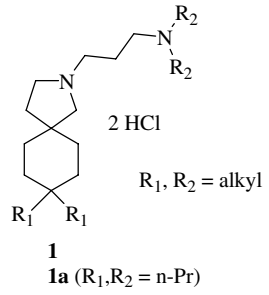
Abstract—With the aid of proposals from a computer program for synthesis design, a new method of synthesizing azaspiranes has been developed. In this method, one starts with a suitable benzoic acid ester, which is subjected to Birch reduction. Then the anionic intermediate is alkylated with 1,2-dibromoethane. The product is subsequently reacted with an amine to give a spiro lactam.

An N-containing spiro structure is one of the important skeletons in pharmaceuticals.[1] In 1973, azaspirane **1** was synthesized by Leonard M. Rice et al. to study its bioactivity, for example, its inhibitory action in KB cells and cells of human mammary cancer grown in tissue culture.[2] Since **1** was disclosed, many related derivatives have been investigated and currently *N*,*N*-diethyl-8,8-dipropyl-2-azaspiro[4,5]decane-2-propanamine **1a** (**1**: $R_1 = n$-Pr, $R_2 = Et$, SK&F106615, Atiprimod) is the compound with the highest reported bioactivity.[3,4] The bioactivities are still being extensively studied.[5] This letter describes a novel route to **1a** (Fig. 1).



1
1a (R_1,R_2 = n-Pr)

Figure 1. General structure of azaspirane and target **1a**.

Two syntheses of **1a** have been published. In one, 4,4-di-*n*-propylcyclohexanone **3** is condensed with ethyl cyanoacetate. The product reacted with KCN via Michael addition. After hydrolysis, the corresponding anhydride **4** reacts with 3-diethylaminopropylamine to provide **1a** by reduction with $LiAlH_4$.[2] Another synthesis consists of a 6-membered ring formation from 4,4-bis-(2-iodoethyl)-heptane **6** and 1-(3-diethylaminopyropyl)-pyrrolidin-2-one **7** followed by $LiAlH_4$ reduction (Scheme 1).[6]

For the purpose of exploration for new efficient synthetic routes, we used the synthesis design program SYNSUP,[7] which generates plausible routes in a retrosynthetic fashion. After a chemist launches the program with a specific goal, there is no further interaction of the program and the chemist. The program explores for routes in a depth first manner. A path leading from the goal is generated step by step. At each stage, the reaction which is judged to produce the most simplification is chosen first, provided it has not been used before at that stage. The greatest simplification means that the most connections present in the final product are made. For example, any cycloaddition reaction would be favored over a single C–C bond forming reaction. The starting compounds of proposed routes must be

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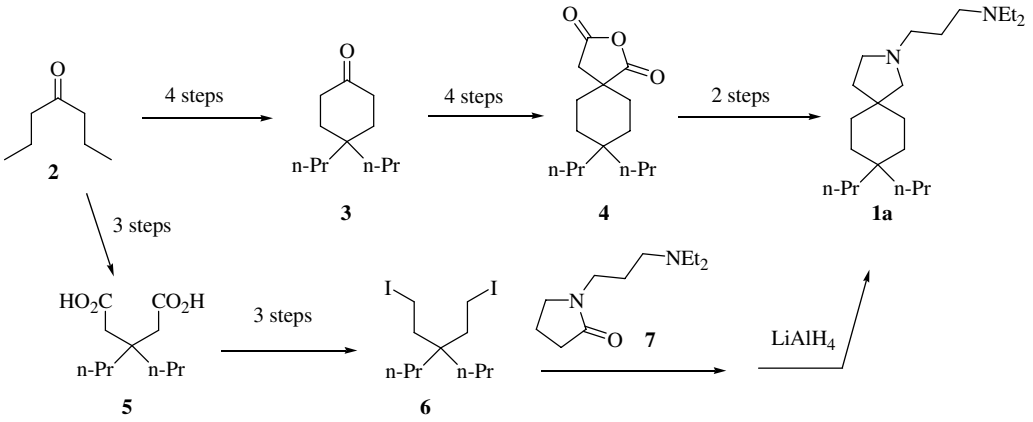


Scheme 1. Two published synthetic routes to **2**, which is one of the most promising biologically active azaspiranes.

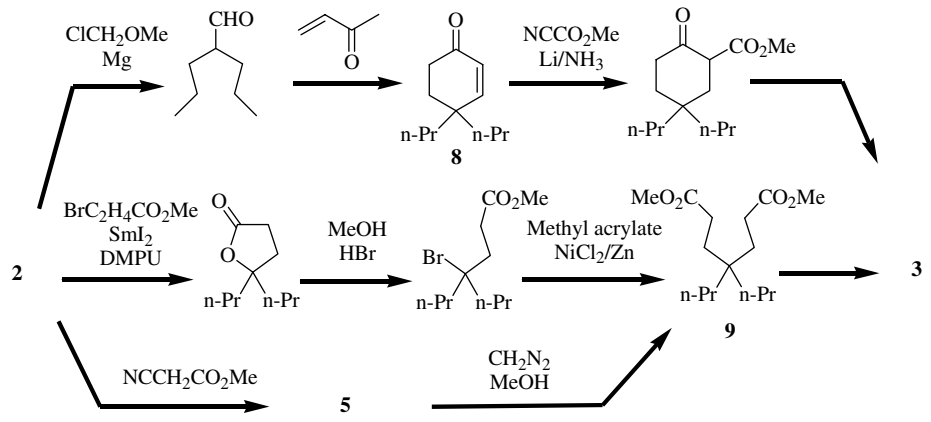
available. This means they should be in a set of catalogs embedded in our program or else they should satisfy the user specified definition of simplicity, such as having a certain limited number of functional groups, of chiral centers, and of rings. In addition, the search can be constrained by compulsory starting materials and/or a specification in the input that certain bonds must or must not be made in the course of an acceptable route. The program has been developed for more than 20 years in order to find manufacturing processes for promising new organic compounds used in the areas of pharmaceutical products, agrochemicals and electronic materials. At the present time, our program has more than 5500 synthetic procedures for generating precursors. In the real world, there are many more synthetically useful transformations than this number, so we are constantly adding more synthetic procedures to the repertory of the program.

We ran the program to see if SYNSUP would produce the reported routes to **1a**. With respect to synthetic routes of the key intermediate **3** from **2**, our program proposed more than one hundred routes including known routes. Scheme 2 shows an interesting excerpt chosen from routes suggested by SYNSUP. We display computer proposed routes with bold arrows, to distinguish them from experimentally accomplished schemes.

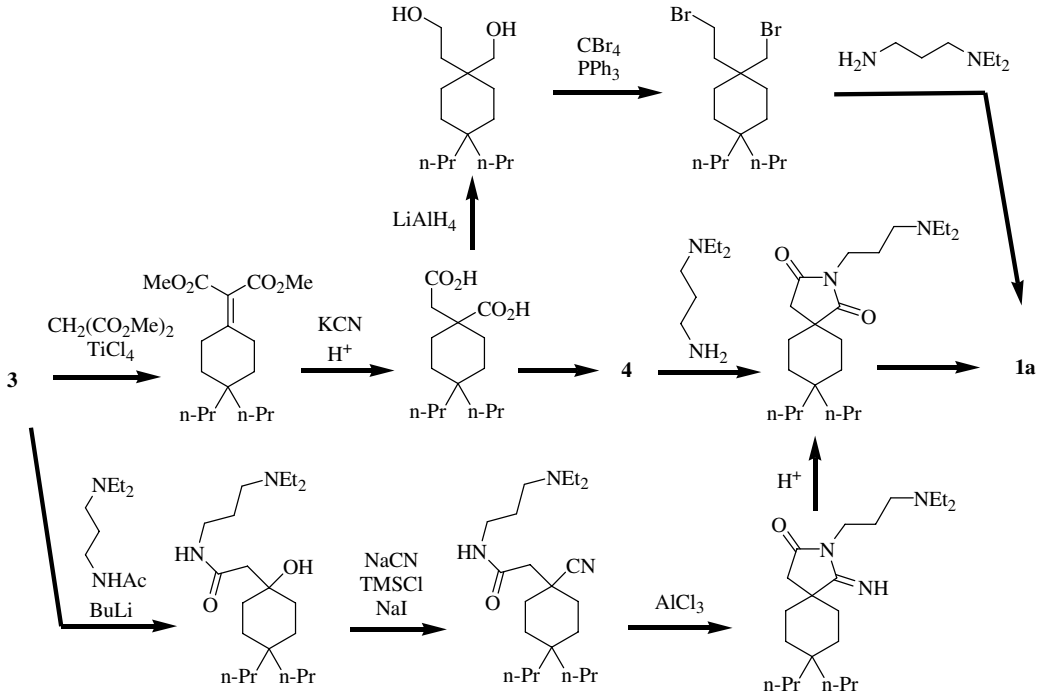
There are two reported routes of **3**: the hydrogenation of **8** and the Dieckmann reaction of dicarbonyl **9**. Although the program did not propose the hydrogenation of **8**, it did propose the principal skeletal transformations in the experimentally achieved routes to **3**. Scheme 3 shows a portion of the synthetic routes of **1a** from **3** proposed by SYNSUP. The routes include the reported route via **4**. From the result of the test, we confirmed that our program generally could suggest the reported routes.

Besides the routes in Scheme 1, routes to [4,5]-azaspiranes via radical cyclization of cyclohexenyl selenocarbamates,[8] CuCl catalyzed cyclization of cyclohexene derivatives substituted with trichloroacetoamides,[9] intramolecular hydroamination of 1-allyl-1-aminomethylcyclohexanes with BuLi,[10] oxidative spirocyclization of phenolic sulfonamides,[11] and irradiation of aminoethylcyclohexanones[12] have been reported.

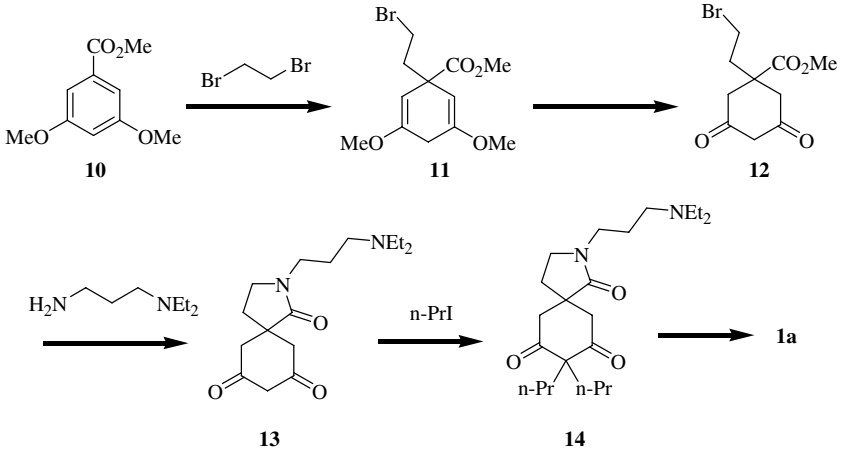
Using the proposals of SYNSUP with a focus on finding a new route of azaspirane, an encouraging synthetic plan was selected as shown in Scheme 4. According to the plan, the commercially available methyl 3,5-dimethoxybenzoate **10** is to be converted via Birch reduction alkylation with 1,2-dibromoethane to cyclohexa-1,3-diene **11**. Hydrolysis of **11** will give **12**, which is then



Scheme 2. Proposed routes of **3** from **2** proposed by SYNSUP.



Scheme 3. Proposed routes of **1a** from **3** proposed by SYNSUP.

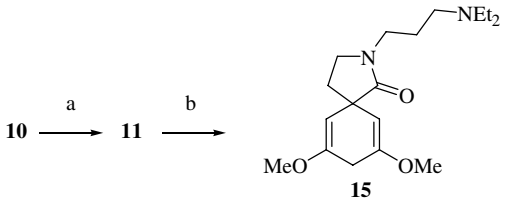


Scheme 4. An encouraging new synthetic route to **1a** proposed by SYNSUP.

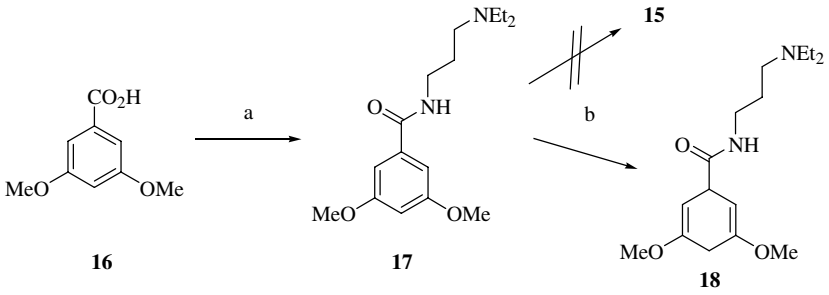
reacted with a diamine to effect ring closure, as shown in Scheme 4. Diketone **13** is doubly alkylated with 2 mol of 1-propyl iodide to give **14**, which is then deoxygenated to give **1a**, the final product.

The plan was confirmed by experiments, done with a slight alteration in the order of operations. The starting material **10** was treated with 1,2-dibromoethane to produce **11** quantitatively. **11** was reacted with the diamine to give **15** via cyclization in moderate yield (Scheme 5).[13]

Incidentally, SYNSUP also proposed another synthetic route for **15**, that is, from **16**. However, the attempted Birch reduction alkylation of benzoyl amide **17** with 1,2-dibromoethane was unsuccessful and only the simply reduced product **18** was obtained in 91% yield (Scheme 6).



Scheme 5. The first part of the experimental route to **1a**. Reagents and conditions: (a) 1. *t*-BuOH, NH_3, Li, THF, −78 °C; 2. $Br(CH_2)_2Br$ (96%) and (b) $H_2N(CH_2)_3NEt_2$, NEt_3, DMF, reflux (70%).

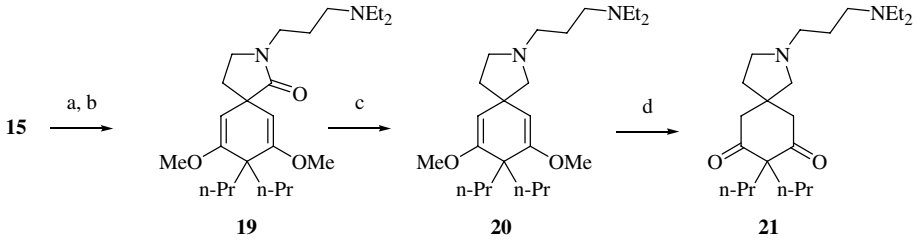


Scheme 6. An unsuccessful trial to generate **15** based on another proposal by SYNSUP. Reagents and conditions: (a) $H_2N(CH_2)_3NEt_2$, DCC, THF (88%) and (b) 1. *t*-BuOH, NH_3, Li, THF, −78 °C; 2. $Br(CH_2)_2Br$ (91%).

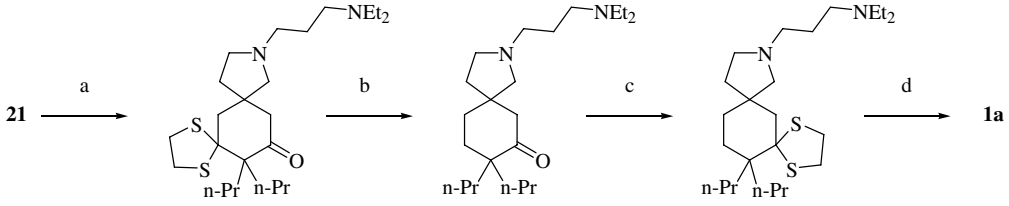
Dialkylation of **15** was done using standard procedures: a THF solution of *n*-BuLi was added to **15** in the presence of HMPA at −78°C. Alkylation with 1-propyl iodide gave **19**, which was reduced by $LiAlH_4$. Deprotection of **20** with acid yielded **21** quantitatively (Scheme 7).[14]

Deoxygenation of **21** proved to be very difficult. Under typical reduction conditions, both the Wolff–Kishner reduction[15] and reduction with $NaBH_3CN$ to the corresponding tosylhydrazone[16] completely failed. Finally, we succeeded via hydrogenation of dithioketals in the presence of Raney nickel. Even using this method, simultaneous conversion of the diketone of **21** into the corresponding bis-dithioketal failed, probably because of steric hindrance. Accordingly, **1a** was obtained by stepwise deoxygenation (Scheme 8).

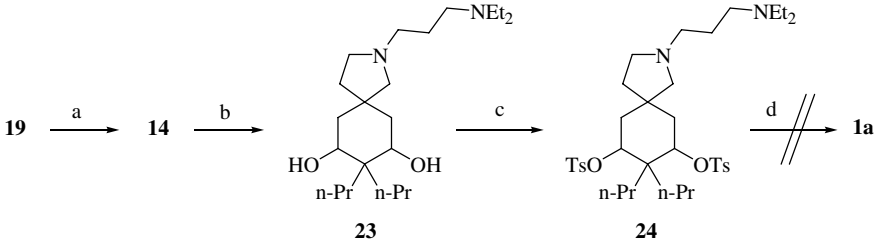
In an effort to decrease the trouble of the deoxygenation, the racemic diol **23** from **19** was converted to tosylate **24** for deoxygenation (Scheme 9). But deoxygenations with $LiEt_3BH$ or $LiAlH_4$[17] did not proceed. In addition, the



Scheme 7. The second part of the experimental route to **1a**. Reagents and conditions: (a) 1. *t*-BuLi, HMPA, THF, −78 °C; 2. *n*-PrI; (b) 1. *t*-BuLi, HMPA, THF, −78 °C; 2. *n*-PrI (quant.); (c) $LiAlH_4$, THF, reflux (93%) and (d) 1 N HCl (95%).



Scheme 8. The successful deoxgenation of **21** to produce the final goal azaspirane **1a**. Reagents and conditions: (a) $HS(CH_2)_2SH$, BF_3–OEt_2, 90 °C (42%); (b) Raney Nickel, EtOH, reflux (39%); (c) $HS(CH_2)_2SH$, BF_3–OEt_2, 90 °C (64%) and (d) Raney Nickel, EtOH, reflux (43%).



Scheme 9. Another failed trial of deoxygenation of diketone via the corresponding diol **23** to **1a**. Reagents and conditions: (a) 1 N HCl, acetone (99%); (b) $LiAlH_4$, THF (91%) and (c) $LiEt_3BH$ or $LiAlH_4$.

attempted photosensitized electron-transfer reaction[18] of the di-*m*-trifluorobenzoate of **23** produced only an intractable mixture.

The overall yield of the six steps from the starting material **10** to diketone **21** was 59%. However, the total yield of **1a** was only 3%, which is lower than the approximately 25% achieved by the reported route in Scheme 1. The low yield was due to the inefficient stepwise deoxygenation and also to the fact that we did not do any optimization of the yields. The computer program does not estimate yields. It attempts to minimize chemically erroneous reaction steps by inspecting the functional groups in the molecule and determining from its stored data whether or not any of them would be damaged by the reagent used. It also notes the influence of aromatic substituents on the orientation of substitution, assesses steric hindrance, etc. At the end, there is a qualitative decision, that is, to proceed with this reaction or not.

In summary, with the aid of the SYNSUP program, a new synthetic route to azaspiranes was found, using Birch reduction alkylation followed by lactamization with an amine.

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13. ^{1}H NMR: δ (ppm), $CDCl_3$, coupling constants J in Hz. Compound **11**: 2.31 (2H, t, $J = 8.3$ Hz), 2.76 (2H, t, $J = 1.5$ Hz), 3.21–3.27 (2H, m), 3.61 (6H, s), 3.69 (3H, s), 4.63 (2H, s). Compound **15**: 1.02 (6H, t, $J = 6.9$ Hz), 1.71–1.75 (2H, m), 2.03–2.08 (2H, m), 2.41–2.57 (6H, m), 2.79–3.00 (2H, m), 3.30–3.41 (4H, m), 3.57 (6H, s), 4.47 (2H, s).
14. ^{1}H NMR: δ (ppm), $CDCl_3$, coupling constants J in Hz. Compound **19**: 0.80–0.85 (6H, m), 0.97–1.03 (3H, m), 1.21–1.26 (2H, m), 1.49–1.57 (4H, m), 1.70–1.76 (2H, m), 2.00 (2H, t, $J = 6.9$ Hz), 2.40–2.56 (6H, m), 3.29–3.39 (4H, m), 3.50 (6H, s), 4.53 (2H, s). Compound **20**: 0.77–0.83 (6H, m), 0.89–1.05 (10H, m), 1.44–1.50 (4H, m), 1.63–1.71 (2H, m), 1.76–1.81 (2H, t), 2.39–2.57 (6H, m), 2.61–2.69 (6H, m), 3.47 (6H, s), 4.75 (2H, s). Compound **21**: 0.83–0.93 (6H, m), 0.96–1.15 (10H, m), 1.53–1.73 (6H, m), 2.32–2.73 (18H, m).
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