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Synthesis of the Marine Sponge Derived β_2-Adrenoceptor Agonist S1319

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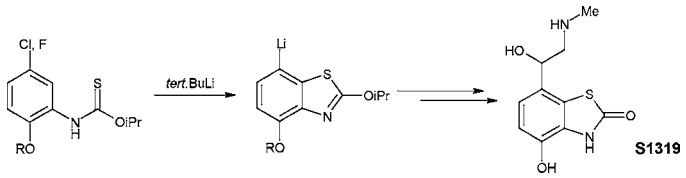
ABSTRACT



The marine sponge derived β_2-adrenoceptor agonist S1319 has been synthesized following a six-step linear sequence. Central to the approach employed is the formation of a 7-lithiated-2,4-dialkoxybenzothiazole intermediate obtained via a directed-lithiation/benzyne-mediated cyclization reaction. The incorporation of a *tert*-butyl ether residue into the cyclization precursor for the pivotal ring-closing step has been shown to significantly increase the efficiency of the reaction by the suppression of a competing directed ortho-lithiation reaction.

Over the past century β_2-adrenoceptor agonists have evolved to become established as one of the front-line treatments for the respiratory conditions asthma and chronic obstructive pulmonary disease. Historically, the principal strategy for refinement of this family of drugs has been achieved through the rational manipulation of the endogenous ligand adrenaline **1**.[1] Following this approach has proven effective, and marked improvements in stability, selectivity, and pharmacological profile have been achieved. This has culminated in the identification of the currently prescribed inhaled long-acting β_2-adrenoceptor agonists formoterol and salmeterol.[2] Presently, the search to identify more effective β_2-adrenoceptor agonists continues with several groups striving to define the next generation of drugs to advance this class.[3] As an alternative strategy, natural products have repeatedly provided the inspiration for new pharmaceuticals.[4] Hence, the disclosure by the Kirin Brewery of the natural product S1319 **2**, isolated from the marine sponge *Dysidea sp.*, and described as a β_2-adrenoceptor agonist of equivalent potency to formoterol attracted our attention as a potential new lead for this therapeutic class.[5] The structural relationship between S1319 and adrenaline is shown in Figure 1. Noteworthy are

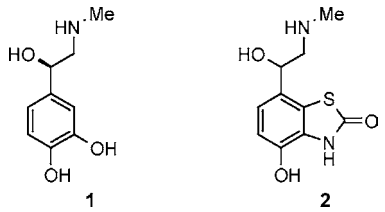


Figure 1. Structures of adrenaline **1** and S1319 **2**.

the common structural elements which indicate that both compounds satisfy the same pharmacophore. The 5-hydroxybenzothiazolone group of **2** mimicks the oxidatively labile catechol moiety of the native hormone.[6] In this Letter we describe our initial studies to define an efficient synthetic route to **2**.

(1) Waldeck, B. *Eur. J. Pharmacol.* **2002**, *445*, 1−12.
(2) Campbell, L. M. *Int. J. Clin. Pract.* **2002**, *56*, 783−790.
(3) (a) Anon *Expert Opin. Ther. Pat.* **2003**, *13*, 273−277. (b) Anon. *Expert Opin. Ther. Pat.* **2004**, *14*, 1385−1388. (c) Cazzola, M.; Matera, M. G.; Lötvall, J. *Expert Opin. Invest. Drugs* **2005**, *14*, 775−783.
(4) Harvey, A. L. *Trends Pharmacol. Sci.* **1999**, *20*, 196−198. *Drug Discovery from Nature*; Grabley, S., Thiericke, R., Eds.; Springer-Verlag: Berlin: Germany, 1999.
(5) Suzki, H.; Shindo, K.; Ueno, A.; Miura, T.; Takei, M.; Sakakibara, M.; Fukamachi, H.; Tanaka, J.; Higa, T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1361−1364.

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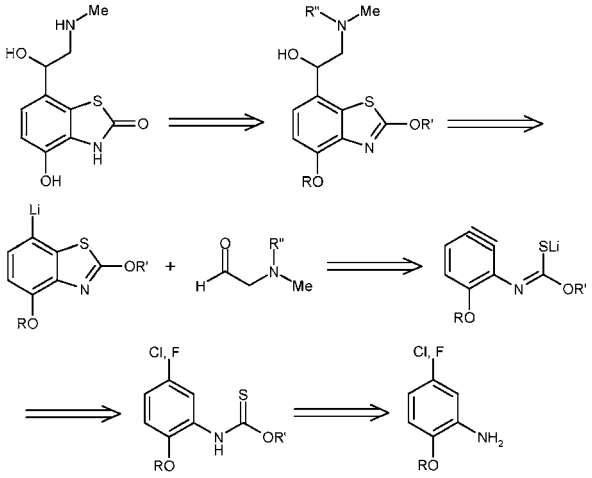
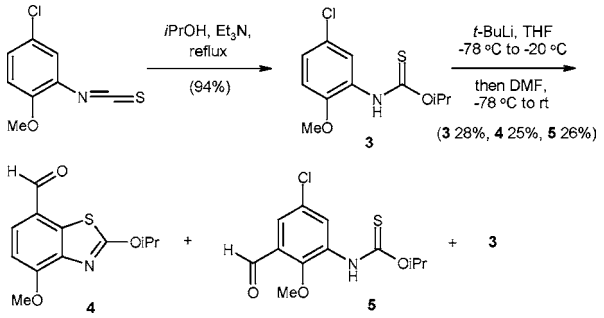
A synthesis of **2** by the isolating group has previously been described in the patent literature.[7] This sequence is based around an electrophilic closure to provide a 7-methylbenzothiazole derivative as a key intermediate. The subsequent manipulation of the 7-methyl residue, through an extended sequence, delivered the required 7-*N*-methylethanolamine functionality of **2** in 12 steps and 0.5% overall yield. More recently a second synthetic approach has been described in the patent literature based upon a Fries rearrangement of 4-bromoacetyloxy-benzothiazolone as the key step to install the two-carbon unit at the 7-position of **2**.[8] We had sought a more efficient route and reasoned that a requirement would be the ability to introduce a more highly functionalized 7-substituent into the benzothiazolone nucleus at the appropriate point in the synthesis. As a way to achieve this, the intramolecular nucleophilic cyclizations of lithiated benzyne thiocarbamates attracted our interest as reported by Stanetty et al.[9] Following such an approach would be anticipated to provide an efficient route to 7-lithiated 2,4-dialkoxybenzothiazole intermediates. The trapping of organometalic species of this type with suitably functionalized electrophiles would provide the potential for direct access to protected versions of the target **2**. Such an approach is outlined in the retrosynthetic analysis shown in Scheme 1.

Scheme 1. Retrosynthetic Analysis of **2**



Our initial investigations toward the synthetic approach proposed above started from the commercially available 5-chloro-2-methoxyphenylisothiocyanate. Conversion of this starting material to the required thiocarbamate cyclization precursor **3** was achieved in a single step by the addition of 2-propanol, as shown in Scheme 2. Exposure of **3** to the

Scheme 2. Preparation and Cyclization of **3**



reported deprotonation/benzyne-mediated cyclization conditions,[9] followed by the addition of DMF produced the desired 7-formylated benzothiazole **4**. Thus, this demonstrated the formation of the desired 7-lithio-2,4-dialkoxybenzothiazole intermediate, and the ability of this anion to react with a model electrophile. However, in addition to the anticipated product **4**, the 3-formylated derivative **5** was also isolated, along with the recovery of unreacted starting material **3**. All three of these components were present in the crude reaction mixture to a similar extent. The byproduct **5** presumably is derived from a competing lithiation ortho to the methoxy group in **3**, rather than the desired in-between deprotonation at the 6-position. Observing such an effective competing deprotonation of **3** was unanticipated based upon the reported efficient cyclization of the equivalent carbamate analogues to 7-lithio-4-methoxybenzoxazole intermediates which indicates that in these doubly activated systems the thiocarbamate group is a less effective functionality for directing ortho-metalation compared to the equivalent carbamate moiety.[10]

As a consequence, we considered ways for rationally improving the selectivity in the above reaction in favor of the 7-lithiated benzothiazole intermediate. To explore this possibility, modifications of the reaction conditions to bias the site of directed ortho-metalation away from the chelation driven 3-position and in favor of both the inductively and chelation driven 6-position were investigated as depicted in Figure 2. In summary, variations of the solvent, base, temperature profile, and the inclusion of anion modifiers were all screened based upon precedents which had been shown to favor either a halogen inductively driven ortho-deprotonation, a chelation assisted lithiated acyl aniline directed ortho-lithiation, or anion equilibrating conditions at temperatures where elimination to the benzyne intermediate would be anticipated to occur.[11] The above modified conditions all failed to either improve the selectivity ratio between **4** and **5** or increase the isolated yield of **4**, compared with the originally reported conditions.[9] Complete consumption of the starting material **3** could be achieved by increasing the

(6) 4-Hydroxybenzothiazolones have previously been employed as catechol mimics in a series of dopamine D_2 agonists, and the dual dopamine D_2/β_2-adrenoceptor agonist sibenadet, see: (a) Weinstock, J.; Gaitanopoulos, D. E.; Stringer, O. D.; Franz, R. G.; Hieble, J. P.; Kinter, L. B.; Mann, W. A.; Flaim, K. E.; Gessner, G. *J. Med. Chem.* **1987**, *30*, 1166−1176. (b) Bonnert, R. V.; Brown, R. C.; Chapman, D.; Cheshire, D. R.; Dixon, J.; Ince, F.; Kinchin, E. C.; Lyons, A. J.; Davis, A. M.; Hallam, C.; Harper, S. T.; Unitt, J. F.; Dougall, I. G.; Jackson, D. M.; McKechnie, K.; Young, A.; Simpson, W. T. *J. Med. Chem.* **1998**, *41*, 4915−4917.

(7) Suzki, H.; Shindo, K.; Ueno, A.; Miura, T.; Takei, M.; Fukamachi, H.; Higa, T. PCT Int. Appl. WO 9909018, 1999.

(8) Okita, T.; Otsuka, N. Jpn. Kokai Tokkyo Koho JP 2005187357, 2005.

(9) Stanetty, P.; Krumpak, B. *J. Org. Chem.* **1996**, *61*, 5130−5133.

(10) Fisher, L. E.; Caroon, J. M. *Synth. Commun.* **1989**, *19*, 233−237.

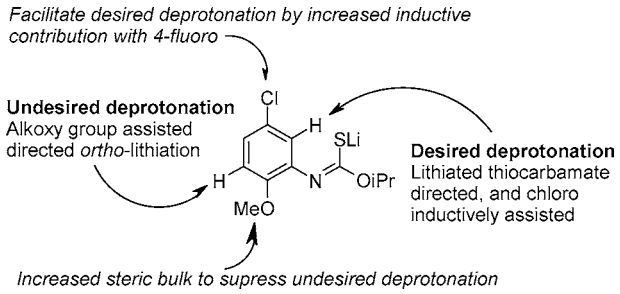


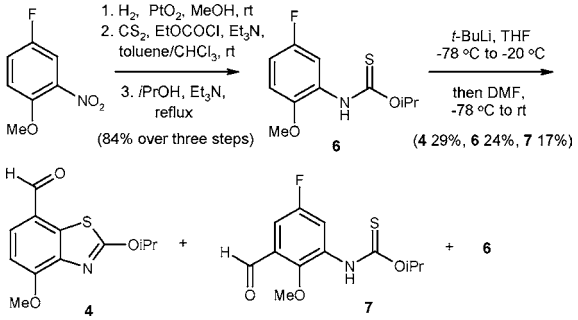
Figure 2. Factors controlling the regioselectivity of deprotonation for the cyclization precursor **3**, and potential strategies for favoring proton removal from the 6-position.

amount of *tert*-butyllithium beyond the 2.8 equiv described for the original procedure. However, this also resulted in what was rationalized as the further reaction of the desired product **4**, involving the displacement of the 2-isopropxy benzothiazole moiety by the *tert*-butyl anion, to give the 2-*tert*-butyl benzothiazole analogue. This resulted in no improvement in the overall efficiency of the reaction, but only in a more tedious chromatographic separation to isolate the products. As a consequence of the above limitations we next turned our attention to an investigation into modifications of the cyclization precursor **3** as a way to enhance the efficiency of the formation of the desired 7-lithiated benzothiazole species.

Two strategies were considered for the modification of the cyclization precursor **3**, as outlined in Figure 2. First switching the 5-chloro to a 5-fluoro substituent was anticipated to enhance the inductive contribution to favor the desired removal of the proton from the 6-position.[12] As a second strategy, increasing the size of the 2-alkoxy residue was reasoned to be a way to stericaly suppress the undesired deprotonation at the 3-position.

To explore the first strategy, the 5-fluoro cyclization precursor **6** was readily prepared in an analogous manner to the equivalent chloro analogue **3**, as shown in Scheme 3. Starting from 4-fluoro-2-nitroanisole, manipulation of the nitro residue by reduction to the aniline, followed by conversion to the isothiocyanate and the addition of 2-propanol gave the desired thiocarbamate cyclization precursor **6**.[13] With **6** in hand, exposure of this material to the reported deprotonation/benzyne-mediated cyclization conditions was

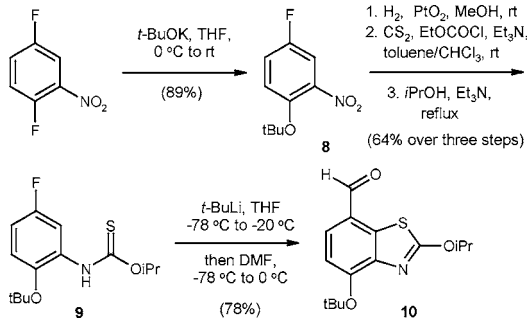
Scheme 3. Preparation and Cyclization of **6**



followed by the addition of DMF.[9] This similarly resulted in the isolation of a mixture of the formylated products **4** and **7**, in addition to the recovery of the starting material **6**. The ratio of these three components in the crude reaction mixture was equivalent to that observed with the 5-chloro analogue **3**. This indicated that the change in the nature of the leaving group at the 5-position seemed to have little effect on the reaction outcome. Hence, we switched our attention to the possibility of steric blockade as a way to suppress the competing proton removal from the 3-position as a more efficient route to the desired 7-lithiated 2,4-dialkoxybenzothiazole intermediate.

An added benefit of the steric blocking approach at the 2-position was anticipated to be the scope for the inclusion of more readily removable protecting groups for the phenolic residue present in the target **2**. To this end, increasing the size of the 2-methoxy group present in **3** and **6** to the level of the *tert*-butoxy analogue, in addition to impeding the undesired reactivity, was additionally anticipated to provide an acid labile functionality for the final phase of the synthesis. To explore this possibility, preparation of the required cyclization precursor was started from 2,5-difluoronitrobenzene, as shown in Scheme 4. Displacement of the more

Scheme 4. Preparation and Cyclization of **9**



activated fluoride from the 2-position of this material occurred efficiently via an S_NAr reaction with potassium *tert*-butoxide to produce the aryl ether **8**.[14] Subsequent reduction

(11) For conditions favoring deprotonation ortho to a halo substituent, or metalated acylated aniline, see: (a) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133−1136. (b) Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett* **1990**, 747−748. (c) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731−732. (d) Takagishi, S.; Katsoulos, G.; Schlosser, M. *Synlett* **1992**, 360−362. (e) Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430−5434. (f) Moro-oka, Y.; Iwakiri, S.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2000**, *41*, 5225−5228. For examples of reaction conditions controlling equilibration between anion species, see: (g) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564−1565. (h) Leonard, N. J.; Bryant, J. D. *J. Org. Chem.* **1979**, *44*, 4612−4616.

(12) Kessar, S. V. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, Chapter 2.3.

(13) Hodgkins, J. E.; Reeves, W. P. *J. Org. Chem.* **1964**, *29*, 3098−3099.

(14) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem.* **1998**, *63*, 9594−9596.

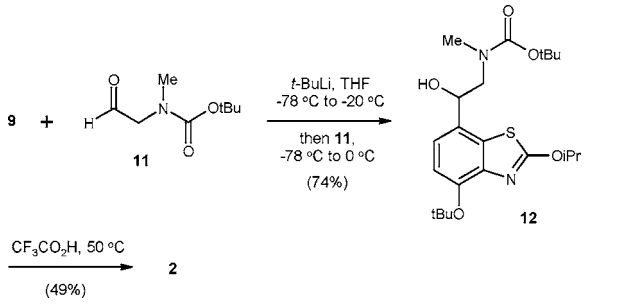
of the nitro residue in **8** was followed by a sequence analogous to that described above for the preparation of the thiocarbamate **6**. This sequence delivered the thiocarbamate cyclization precursor **9** in 57% overall yield for the four steps. As done previously, exposure of **9** to the reported deprotonation/benzyne-mediated cyclization conditions was followed by quenching of the anion by the addition of DMF.[9] Interestingly, in contrast to the 2-methoxy analogues of **9**, this modification now delivered the 7-formylated benzothiazolone **10** as the predominant product. ^{1}H NMR analysis of the crude reaction mixture showed no evidence for the presence of significant quantities of the uncyclized 3-formylated byproduct, equivalent to **5** and **7**. Additionally, consumption of the starting material **9** was essentially complete in this reaction, with the aldehyde **10** being isolated in 78% yield.

With an efficient route to the 7-lithiated 2,4-dialkoxybenzothiazole anion identified, we turned our attention to reaction partners that would enable the introduction of the required functionality into the 7-position of the natural product **2**. To achieve this, the readily prepared Boc-protected sarcosine derived aldehyde **11** was anticipated to be suitable for the introduction of a protected form of the desired *N*-methylethanolamine residue directly.[15] Thus, generation of the 7-lithiated benzothiazole intermediate from **9**, as described above, was followed by addition of the electrophile **11**. This reaction delivered the anticipated benzylic alcohol **12** in 74% isolated yield, as shown in Scheme 5. Finally, global deprotection of **12** was then readily achieved upon treatment with trifluoroacetic acid to give the target molecule **2**.[16]

(15) Kato, S.; Harada, H.; Morie, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3219−3225.

(16) Comparison of the spectroscopic data obtained for **2**, as the trifluoroacetate salt, was consistent with that reported for the natural product S1319 described in refs 5 and 7.

Scheme 5. Completion of the Synthesis of **2**



In summary, the marine natural product **2** has been prepared in racemic form following a six-step linear sequence in 20% overall yield. The key step for this approach made use of a directed-lithiation/benzyne-mediated cyclization, which enabled the rapid introduction of a highly functionalized substituent into the 7-position of the benzothiazolone nucleus. To maximize the efficiency of this pivotal cyclization, the incorporation of a *tert*-butyl aryl ether residue was used as a means to sterically suppress a competing directed ortho-lithiation reaction. With an efficient synthetic route in-hand, future studies will concentrate on exploring the potential of the β_2-adrenoceptor agonist **2** as a led for the further advancement of this therapeutic class.

Acknowledgment. The authors thank Dr. Brian Everatt and Dr. John Tyler for analytical support.

Supporting Information Available: Experimental procedures and spectroscopic data for the sequence leading to **2** and the model studies with **3**, **6**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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