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Pictet−Spengler Based Synthesis of a Bisarylmaleimide Glycogen Synthase Kinase-3 Inhibitor

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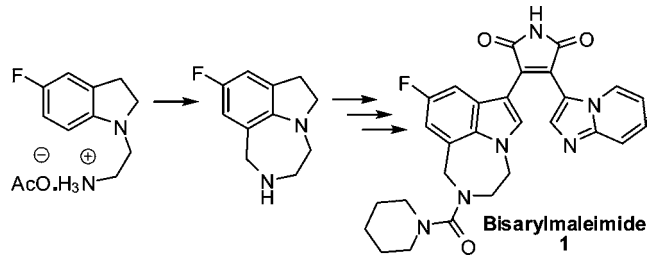
ABSTRACT



A practical synthesis of the glycogen synthase kinase-3 (GSK3) inhibitor bisarylmaleimide 1 has been accomplished employing Pictet−Spengler methodology to access the indole 7-position in preparing the benzodiazepine tricyclic fragment. A seven-step linear sequence that starts with commercially available 5-fluoroindole 7 affords the bisarylmaleimide 1 in 33% overall yield.

Type 2, or noninsulin-dependent, diabetes mellitus accounts for approximately 90% of all cases of diabetes and is characterized by an inability of the body to effectively respond to insulin secreted by the pancreas, or insulin resistance.[1] Glycogen synthase kinase-3 inhibitor (GSK3) is involved in signaling from the insulin receptor. Inhibitors of GSK3 are expected to effect lowering of plasma glucose similar to insulin, making GSK3 an attractive target for the treatment of type 2 diabetes. The GSK3 inhibitor bisarylmaleimide **1**, illustrated in Figure 1, has been studied at Lilly for the treatment of type 2 diabetes.[2]

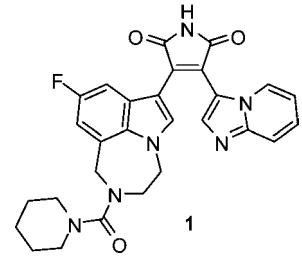


Figure 1. Bisarylmaleimide **1**.

The published synthesis of bisarylmaleimide **1** by Engler and Henry et al. describes the preparation of the tricyclic ring system of the indole fragment via the Bartoli indole synthesis.[2,3] The Bartoli reaction gives access to an indole with an aldehyde at the 7-position for subsequent preparation of the required seven-membered benzodiazepine type ring system.

(1) (a) Cohen, P.; Frame, S. *Nat. Rev. Mol. Cell. Biol.* **2001**, *2*, 769. (b) Cohen, P.; Goedert, M. *Nat. Rev. Drug. Disc.* **2004**, *3*, 479.

(2) Engler, T. A.; Henry, J. R.; Malhotra, S.; Cunningham, B.; Furness, K.; Brozinick, J.; Burkholder, T. P.; Clay, M. P.; Clayton, J.; Diefenbacher, C.; Hawkins, E.; Iversen, P. W.; Li, Y.; Lindstrom, T. D.; Marquart, A. L.; McLean, J.; Mendel, D.; Misener, E.; Briere, D.; O'Toole, J. C.; Porter, W. J.; Queener, S.; Reel, J. K.; Owens, R. A.; Brier, R. A.; Eessalu, T. E.; Wagner, J. R.; Campbell, R. M.; Vaughn, R. *J. Med. Chem.* **2004**, *47*, 3934.

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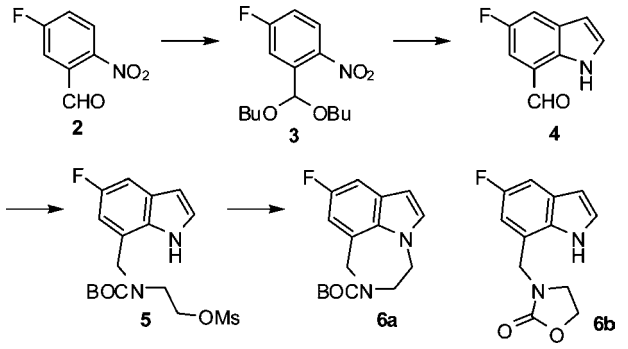
The synthesis starts with 5-fluoro-2-nitrobenzaldehyde **2**, which is prepared via reduction and oxidation of the corresponding acid (Scheme 1).[2,4] 5-Fluoro-2-nitrobenzaldehyde **2** is converted to the di-*n*-butyl acetal **3**, which gives the necessary steric bulk to favor the Bartoli reaction.[3c] The Bartoli reaction and subsequent hydrolysis affords 5-fluoro-7-formylindole **4**. The 7-formylindole **4** is elaborated via reductive amination with ethanolamine, BOC protection, and activation as a mesylate **5** to promote closure of the 7-membered ring to afford **6a**. The intermediate mesylate **5** has stability issues due to intramolecular attack of the BOC group on the mesylate, which gives appreciable amounts of oxazolidinone **6b** at temperatures above 0 °C.[5] In addition, protection group chemistry is necessary since attempts to replace the BOC group with the required piperidine urea of **1** failed to give the desired mesylate activation for 7-membered ring closure.

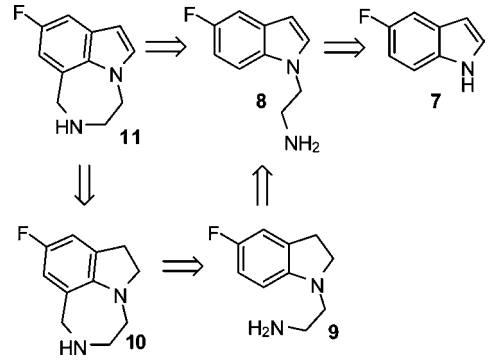
Scheme 1. Intermediates for Bartoli-Based Synthesis of **6a**



To avoid the low temperature Bartoli reaction conditions (≤−40 °C) that require a large excess of vinyl Grignard reagent (4 equiv) and afford modest yields (~50%), we first focused on alternative methods for preparing the tricyclic indole component. Secondary goals were to maximize efficiency by avoiding protection group chemistry and to delay construction of the bisarylmaleimide until late in the synthesis. Bisarylmaleimides are insoluble in most solvents, making them difficult to manipulate and purify. Therefore, a strategy involving late construction of the bisarylmaleimide ring system made sense to increase flexibility of solvent and reagent choices during the synthesis and enhance the purity of the final product.

With these goals in mind, Pictet−Spengler methodology to access the indole 7-position in preparing the benzodiazepine portion of **1** was proposed (Scheme 2). In Scheme 2, the starting 5-fluoroindole **7** is commercially available and has been prepared via the Leimgruber−Batcho method,[6] Fischer indole synthesis with 4-fluorophenylhydrazine and pyruvic acid followed by decarboxylation,[7] and metalation methods by Schlosser.[8] Alkylation of **7** with 2-chloroethylamine to give intermediate **8** has precedence utilizing a quaternary ammonium salt to promote phase-transfer chemistry.[9] Next, we speculated that indole **8** with the ethylamine tether could be taken directly into a Pictet−Spengler cyclization to give tricycle **11** based on literature precedent employing paraformaldehyde and TFA at reflux.[10] If the conversion of **8** to **11** failed, the alternative path of reducing the 5-member indole ring of **8** to the indoline **9** to induce aniline-type direction and promote the Pictet−Spengler cyclization to give tricycle **10** is also precedented.[9b,11] Lastly, the oxidation/dehydrogenation of *N*-alkylated indolines similar to **10** to afford indoles can be accomplished by a variety of methods.[12]

Scheme 2. Retrosynthetic Plan for a Tricyclic Indole



The *N*-alkylation of indole **7** with 2-chloroethylamine hydrochloride **12** performed most reliably in the presence of excess 85% KOH pellets at about 23 °C (Scheme 3). Lesser amounts of KOH, or use of the powdered form, often gave stalled reactions and over alkylation. Research into this matter led to the conclusion that the desired selective monoalkylation was taking place on the surface of the base (85% KOH pellet) in the omega phase.[13] Therefore, the use of excess 85% KOH pellets ensured that an omega phase was

(3) (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129. (b) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* **1991**, 657. (c) Dobson, D. R.; Gilmore, J.; Long, D. A. *Synlett* **1992**, 79.

(4) Lautens, M.; Fang, Y.-Q. *J. Org. Chem.* **2008**, *73*, 538.

(5) Curran, T. P.; Pollastri, M. P.; Abelleira, S. M. R. J.; McCollum, T. A.; Rowe, C. G. *Tetrahedron Lett.* **1994**, *35*, 5409.

(6) (a) Clark, R. D.; Repke, D. B. *J. Heterocycl. Chem.* **1985**, *22*, 121. (b) Madge, D. J.; Hazelwood, R.; Iyer, R.; Jones, H. T.; Salter, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 857.

(7) (a) Bergmann, E. D.; Pelchowicz, Z. *J. Chem. Soc.* **1959**, 1913. (b) Bratulescu, G. *Tetrahedron Lett.* **2008**, *49*, 984.

(8) Schlosser, M.; Ginanneschi, A.; Leroux, F. *Eur. J. Org. Chem.* **2006**, *13*, 2956.

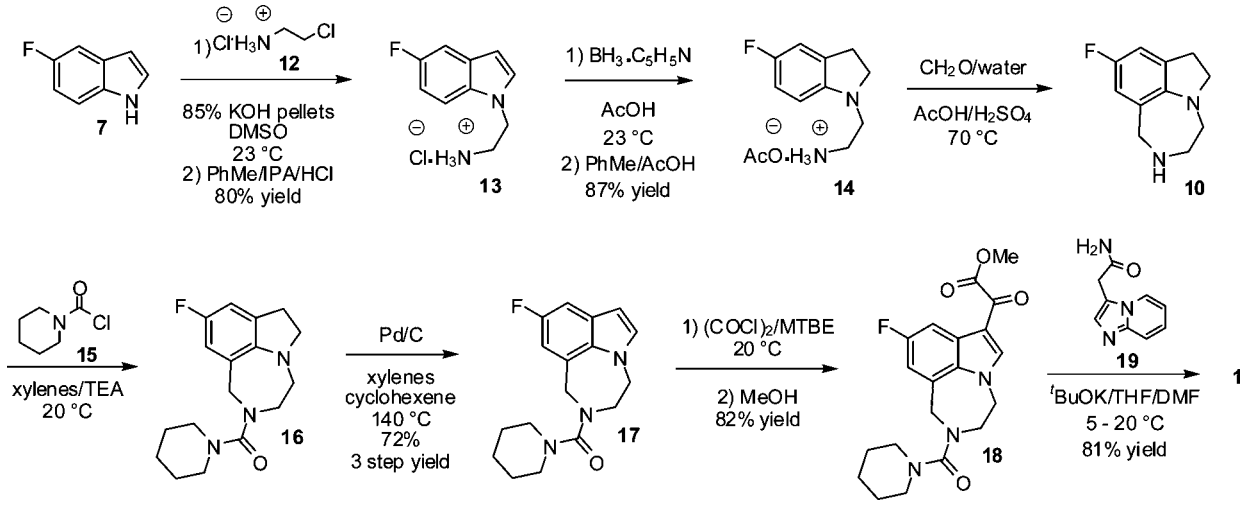
(9) (a) Cuadro, A. M.; Matia, M. P.; Garcia, J. L.; Vaquero, J. J.; Alvarez-Builla, J. *Synth. Commun.* **1991**, *21*, 535. (b) Welmaker, G. S.; Sabalski, J. N. *Tetrahedron Lett.* **2004**, *45*, 4851.

(10) Zhang, L.-H.; Meier, W.; Wats, E.; Costello, T. D.; Ma, P.; Ensinger, C. L.; Rodgers, J. M.; Jacobsen, I. C.; Rajagopalan, P. *Tetrahedron Lett.* **1995**, *36*, 8387.

(11) (a) Archer, S.; Lewis, T. R.; Unser, M. J.; Hoppe, J. O.; Lape, H. *J. Am. Chem. Soc.* **1957**, *79*, 5783.

(12) (a) Naruto, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1980**, *28*, 900. (b) Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636. (c) Hara, T.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 6207. (d) Hara, T.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 6207. (e) Kamata, K.; Kasai, J.; Yamaguchi, K.; Mizuno, N. *Org. Lett.* **2004**, *6*, 3577. (f) Lakatosh, S. A.; Luzikov, Y. N.; Preobrazhenskaya, M. N. *Tetrahedron* **2005**, *61*, 8241. (g) Haider, N.; Kaeferboeck, J. *Tetrahedron* **2004**, *60*, 6495.

Scheme 3. Pictet−Spengler Based Synthesis of Bisarylmaleimide **1**



maintained which afforded high conversions to the desired mono-alkylated indole **13**. Maintaining the reaction temperature at about 23 °C was also important for high conversions to **13** due to competitive degradation of **12** to aziridine, which was more pronouced at higher temperatures. The *N*-akylated indole **13** was purified via isolation as a hydrochloride salt in 80% yield.

The reduction of indole **13** to indoline **14** was attempted via hydrogenolysis with palladium and platinum which typically gave unreliable conversions and over reduction, respectively.[9b,14] The use of triethylsilane in TFA was useful for the transformation of **13** to **14**, but working up the corrosive TFA reaction media to isolate the product was not desirable.[15] Reduction of **13** to **14** was most productive with borane pyridine complex in AcOH at 23 °C.[16] The indoline **14** was first isolated as a hydrochloride salt, but chloride was found to suppress the subsequent Pictet−Spengler chemistry presumably via the formation of stable chlorohydrins. However, **14** could be purified and isolated in 87% yield as an acetate salt which was compatible with the reaction media for the next step.

Attempts to induce Pictet−Spengler cyclizations at the indole **13** oxidation state failed in our hands probably due to the electron deficiency of the fluorinated benzenoid ring. However, the indoline **14** underwent smooth transformation to the tricyclic indoline **10** in the presense of 1 equiv of formalin, AcOH, and catalytic H_2SO_4 at 70 °C. The tricyclic indoline **10** was isolated as an oil and was found to perform best in the necessary oxidation/dehydrogenation to give an indole if the piperidine urea was installed first. With that, **10** was dissolved in xylenes and treated with TEA and 1-piperidinecarbonyl chloride **15** at 20 °C to afford indoline urea **16** as an oil. After workup, the xylenes solution of **16** was treated with palladium on carbon, and cyclohexene was introduced to remove hydrogen from the system and suppress reversion of **17** to **16**. Heating this mixture to 140 °C produced the indole **17** as a crystalline solid in 72% yield from **14**.

The tricyclic indole urea **17** was suspended in MTBE at about 3 °C, and oxalyl chloride was added to the mixture. It was necessary to warm this suspension to 20 °C to induce acylation of the indole 3-position. The suspension was cooled to 10 °C and a large excess of MeOH added to the reaction to generate the methyl ester **18** still as a suspension.[17] At that point, the ester **18** could be isolated by simple filtration and washing with MeOH in 82% yield.

The ester **18** was combined with the known amide **19**[2] in DMF, and the resulting slurry was cooled to about 5 °C. A solution of ᵗBuOK in THF was added to the ester **18**/amide **19** mixture at 5−7 °C to give a homogeneous solution. It was important to keep the temperature at or below 5−7 °C during the base addition as the intermediate imide **20** formed and cyclized via an intramolecular Perkin-type condensation to give **21**, which is slow to dehydrate to the biarylmaleimide **1** (Scheme 4).[17] If the base addition was conducted at higher temperatures, the dehydration event that liberates KOH started to occur prior to completion of the initial imide formation resulting in considerable hydrolysis of the starting ester **18** and loss of desired product yield. After the maleimide formation was complete, the resulting slurry was diluted with water and DMF, and the THF was removed from

(13) (a) Halpern, M. E. In *Phase-Transfer Catalysis: Mechanisms and Syntheses*; Liotta, C. L., Berkner, J., Wright, J., Fair, B., Eds.; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; pp 29−40. (b) Yadav, G. D.; Jadhav, Y. B. *Org. Process Res. Dev.* **2003**, *7*, 588.

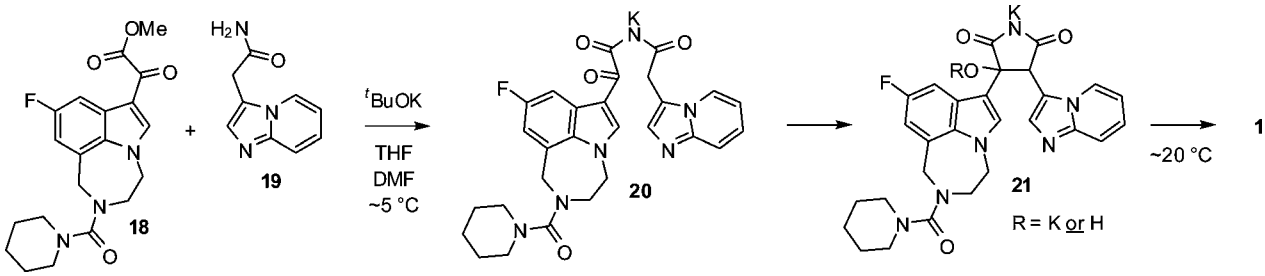
(14) Shaw, J. E.; Stapp, P. R. *J. Heterocycl. Chem.* **1987**, *24*, 1477.

(15) (a) Lanzilotti, A. E.; Littell, R.; Fanshawe, W. J.; McKenzie, T. C.; Lovell, F. M. *J. Org. Chem.* **1979**, *44*, 4809. (b) Magnus, P.; Gallagher, T.; Schultz, J.; Orr, Y.-N.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987**, *109*, 2706. (c) Hobson, L. A.; Nugent, W. A.; Anderson, S. R.; Deshmukh, S. S.; Haley, J. J.; Liu, P.; Magnus, N. A.; Sheeran, P.; Sherbine, J. P.; Stone, B. R. P.; Zhu, J. *Org. Process Res. Dev.* **2007**, *11*, 985.

(16) Yasuo, K.; Kunio, S.; Schun-ichi, Y. *Synthesis* **1978**, 447.

(17) (a) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053. (b) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *Tetrahedron Lett.* **1999**, *40*, 1109.

Scheme 4. Mechanism for Maleimide Formation



the mixture via distillation (failure to remove THF from the system resulted in complex mixed solvates of the crystals of **1** during the isolation/purification). The resulting mixture was quenched with aqueous AcOH and seeded with **1** during a further water addition to induce crystallization of **1** in 81% isolated yield with >99% purity.

The seven-step linear sequence detailed in Scheme 3 that starts with commercially available 5-fluoroindole **7** affords the bisarylmaleimide **1** in 33% overall yield. This linear sequence can be run in standard reactors with no need for temperatures below about 0 °C. There is no protection group chemistry, and the assembly of the insoluble maleimide structure is reserved until the last step which gives flexibility with regards to reagent and solvent choices and ensures high purity final product. The overall result is an efficient and reliable synthesis that provides access to large quantities of the bisarylmaleimide **1**.

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Supporting Information Available: Experimental procedures and spectral data for compounds **13**, **14**, **10**, **16**−**18**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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