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Modular Synthesis of Candidate Indole-based Insulin Mimics by Claisen Rearrangement

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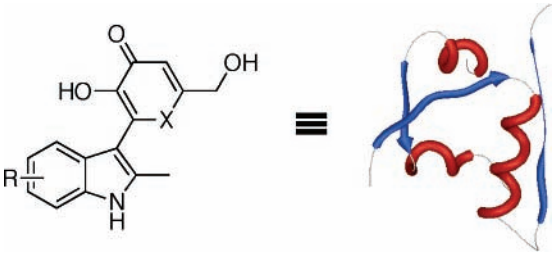
ABSTRACT



A modular synthetic route to (indolyl)kojic acid anti-diabetes agents has been developed. Sonogashira coupling of a protected iodoaniline with a propargyl kojate was used to construct an (indole)methyl kojate. Its heteroaromatic Claisen rearrangement, followed by tautomerization to return the indole and pyrone rings, was used to create the biaryl C–C bond. This route should enable collections of insulin mimic drug candidates to be prepared from a few basic building blocks.

A defining event in medicine occurred at the University of Toronto in 1922, when Banting and Best and their co-workers first successfully administered purified insulin by injection to relieve diabetes symptoms in a patient.[1] Insulin represents the first therapeutic human protein, foreshadowing the many protein therapeutics derived through biotechnology that are used in medicine today. Though alternative orally acting medicines to control blood glucose in Type 2 diabetes have been developed,[2] many Type 2 diabetics remain wedded to daily insulin injections. For Type 1 diabetics, the only alternative to insulin injections was inhaled insulin,[3] no longer marketed.

A potentially important event in diabetes therapy was the 1999 report of the natural product demethylasterriquinone B1 (Figure 1), which mimics the effects of insulin in controlling blood glucose in mouse models of diabetes and as a small molecule is orally active.[4] Significant research following on this discovery[5] identified improved agents that reached the stage of testing in rats, dogs, and primates.[6] Work

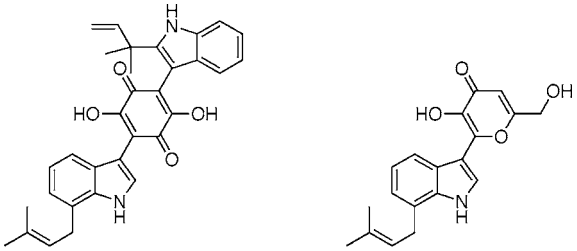


Figure 1. The natural product demethylasterriquinone B1 was originally discovered as an oral insulin mimic. An analog replacing the quinone with kojic acid was recently shown to retain insulin-mimicking bioactivity.[11]

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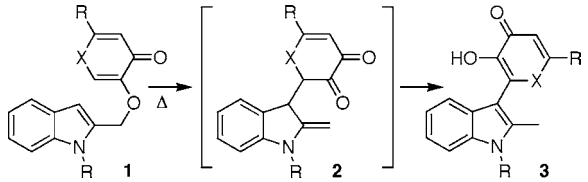
at Merck[7] and in our laboratory[8] defined structure−activity relationships (SAR) in the asterriquinone insulin mimics and identified the quinone and the 7-prenyl indole portions as the pharmacophore. Subsequently, we discovered novel substitution patterns that led to cell-based[9] and orally active[10] insulin mimics.

The discovery of demethylasterriquinone B1 also represented one possible solution to a "grand challenge" of medicinal chemistry: a small molecule that mimics the action of a therapeutic protein. The virtues of traditional pharmaceuticals, including lower manufacturing costs, greater stability during transportation and storage, and easier administration, would make small molecule drugs far superior to proteins if they were available to treat the conditions currently treated with protein therapeutics. Despite the aforementioned attractions, new chemical entities based on the natural product demethylasterriquinone B1 have not reached clinical testing in humans. One concern about these compounds is surely related to their quinone substructure. Although quinones can be found in drug substances administered acutely, as in anti-cancer and anti-infective therapies, this quinone might be more problematic under the long-term administration required for a metabolic disease like diabetes. Further, the protein that these compounds would replace *is* the natural hormone (though administered in an unnatural way). This fact undoubtedly raises the demands for safety of any insulin replacement beyond those required for many investigational new drugs.

In responding to this perceived difficulty, we recently developed replacements for the quinone in the natural product lead compound that maintain insulin mimicry.[11] We described a kojic acid derived demethylasterriquinone B1 analog (Figure 1) and a related pyridone that are insulin mimics in cell-based assays. Preliminary broad-based pharmacological screening of the (indolyl)kojic acid suggests it does not present intrinsic safety issues. This compound therefore constitutes a lead structure for further modification to optimize biological activity. However, structural variation of the indole portion was difficult because our route to these compounds was not very versatile. Our synthetic strategy required reexamination.

We have now developed a synthetic route to (indolyl)-kojic acids based on the Claisen rearrangement of an (indole)-

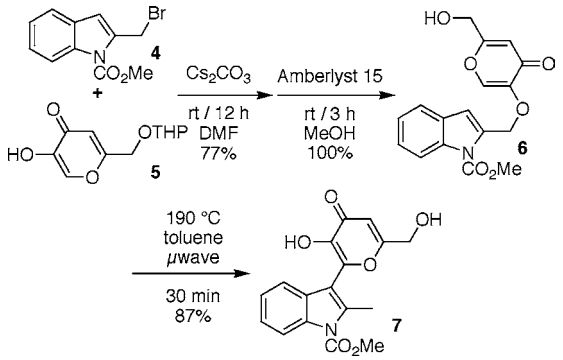
Scheme 1. Claisen Rearrangement of (Indole)methyl Kojates



methyl kojate (Scheme 1). This transformation is on the one hand precedented in the Claisen rearrangement of allyl kojates[12] but is on the other hand unprecedented: this reactant is an analog of benzyl vinyl ether, for which the Claisen rearrangement is unknown.[13] However, such reactions can occur when the benzyl fragment is part of a heteroaromatic ring or when the reactants are electronically biased.[14] Tautomerization of **2** following Claisen rearrangement brings the indole and 4-pyrone back into conjugation, creating a biaryl **3**. A consequence of this strategy is the introduction at the indole 2-position of a methyl group not present in the lead structure. However, our SAR work showed that methyl substitution at this position increases potency slightly.[8]

The preparation of a reactant to test this plan used known compounds **4**[15] and **5**.[16] Following alkylation of the kojic acid, the THP group can be removed and **6** subjected to pyrolysis (sealed reaction vessel, CEM Discover microwave reactor, IR temperature monitoring). The (indolyl)kojic acid **7** is produced efficiently (Scheme 2). This Claisen reaction

Scheme 2. Test of Claisen Approach to (Indolyl)kojic Acids



requires the indole nitrogen to be protected with an electron-withdrawing group, as it is in **6**. When the nitrogen is not

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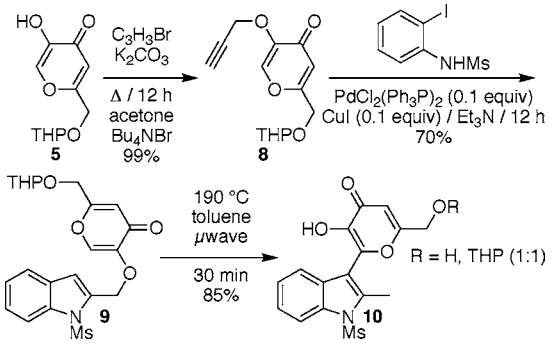
protected, the major product from heating is the kojic acid **5** (10:1 ratio to the Claisen product). Solvolysis of the (indole)methyl kojate presumably occurs when the carbamate is absent, as precedented in the work of Raucher.[14c]

Following demonstration of the key Claisen rearrangement, the final requirement for broad application of this synthetic approach to insulin mimic candidates is quick access to (indole)methyl kojates not involving halides like **4**, whose available structural diversity is limited. Compound **5** can be efficiently converted (Scheme 3) to its propargyl derivative

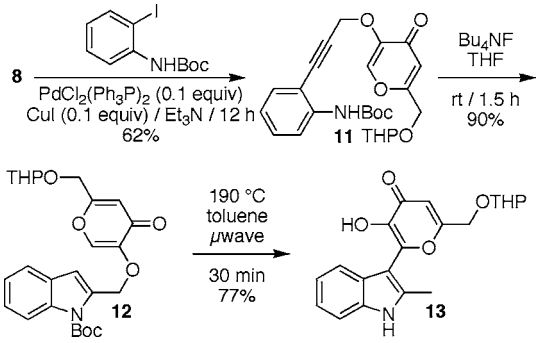
Scheme 3. Modular Preparation of Claisen Substrate



8, which is coupled with *o*-iodoaniline sulfonamide by the Sonogashira reaction. With *N*-methanesulfonyl protection, the coupling product spontaneously cyclizes to the indole and **9** is obtained in 70% yield. Its pyrolysis as before delivers **10** (with partial removal of the THP group).

To obtain the 1*H*-indole goal structures for biological testing would require a possibly challenging removal of an indole *N*-sulfonamide from **10**. We therefore switched to the more easily removed Boc protecting group in further developing the route (Scheme 4). Coupling **8** with *N*-Boc-

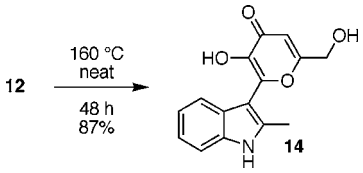
Scheme 4. Synthesis of (Indolyl)kojic Acid **13**



o-iodoaniline provides **11**. Cyclization of such aniline-derived Sonogashira coupling products to the indoles can be spontaneous under the coupling conditions[17] or can be performed with other metallic catalysts, primarily palladium[18] but also gold,[19] platinum,[20] copper,[21] indium,[22] or potassium *tert*-butoxide.[23] We found that **11** rapidly and efficiently cyclizes to (indole)methyl kojate **12** on treatment with tetrabutylammonium fluoride (TBAF).[24]

The (indolyl)kojic acid **13** in which the Boc group had been removed was obtained upon microwave heating of **12** in toluene under the conditions depicted earlier. This process presumably occurs via initial Claisen rearrangement followed by removal of the protecting group, since our earlier work showed that an electron-withdrawing group on the indole nitrogen is essential to prevent solvolysis of the (indole)-methyl kojate. Supporting this idea is the fact that heating **12** conventionally in toluene at reflux overnight gives the Claisen rearrangement product retaining the Boc group (not shown). We suggest that the removal of the Boc group in the microwave reaction occurs via initial loss of isobutylene via a Cope elimination. Supporting this idea is the fact that when the Boc group is exchanged for a (methoxy)carbonyl group (not shown), this protecting group is retained following Claisen rearrangement (87%).We then examined the influ-

Scheme 5. Boc/THP Group Removal by Extended Heating



ence of reaction conditions on the Claisen rearrangement of **12**. Because high temperatures are needed and we aimed to avoid difficult-to-remove high-boiling solvents, reactions were performed neat in an open flask, using conventional oil bath heating. Heating **12** at 160 °C for 3 h provides **13** in 95% yield. Taking a cue from our earlier observation that the thermal rearrangement of sulfonamide **9** partially deprotects the THP group, the reaction time was extended. As THP removal is potentially reversible, free access to the atmosphere permits the evaporation of dihydropyran or its derived products. Prolonged heating delivers the ultimate target of this route, **14**, in excellent yield.

With these results as a guide, a general modular route to substituted (indolyl)kojic acids was developed (Scheme 6). A variety of 4-substituted *o*-iodoanilines can be converted to their Boc derivatives **15**{***n***} via standard protocols.

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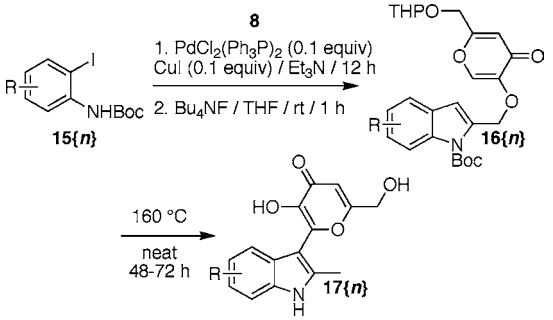
Scheme 6. Preparation of Diverse (Indolyl)kojic Acids **17**



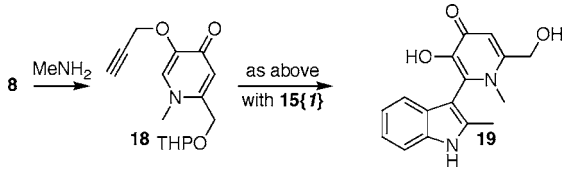
Sonogashira reaction with **8** followed by the addition of tetrabutylammonium fluoride directly to the reaction mixture provides 5-substituted indoles **16**{***n***}. Upon heating, these materials are converted to the targets **17**{***n***}. This process requires only two pots and creates rather complex molecules from simple starting materials: a Boc-iodoaniline and a propargyl kojate, each readily prepared. Results are summarized in Table 1.

Table 1. Results from Application of the Route in Scheme 6 to Substituted *o*-Iodoaniline Derivatives **15**

entry and ***n***	R	yield of **16**{***n***}	yield of **17**{***n***}
1	H	55	87
2	4-Cl	61	73
3	4-CO_2Me	60	70
4	4-CN	70	63
5	4-Me	69	70

The process as described so far effectively incorporates structural diversity into the indole portion of the targets. It is also useful for varying the kojic acid portion (Scheme 7),

Scheme 7. Diversifying the Kojic Acid with Pyridone **18**



setting the stage for a full exploration of substituent effects on the biological properties of (indolyl)kojic acids. The conversion of **8** to pyridone **18** can be performed by treatment with methylamine under slightly acidic conditions. Sonogashira coupling with **15**{***1***} (68% yield) and Claisen rearrangement as before give product **19** (53%).

In sum, we have developed a modular synthetic route to (indolyl)kojic acid derivatives that should permit the preparation of libraries of diverse structures as candidate insulin mimics. It avoids the preparation of unstable organotin reagents involved in our earlier syntheses of such compounds.[11] One limitation to the route is that it requires iodoanilines or other similarly reactive nitrogen-substituted arenes. Attempts to use protected *o*-bromoanilines in the Sonogashira coupling have so far been unsuccessful, but novel methods to achieve this transformation have lately become available.[25]

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Supporting Information Available: NMR spectra for new compounds and other experimental and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800058D

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