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Progress Toward the Total Synthesis of Psymberin / Irciniastatin

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Abstract

In this publication, we describe our synthesis of four key building blocks for the total synthesis of psymberin (**1**) and its C4 epimer (**2**). Despite early difficulties in processing material to the advanced intermediate stage, we have been successful in developing high-yielding syntheses for the pyran core, natural sidechain, 4-epi sidechain and aryl fragments of the molecule. Our findings from the optimization process are presented herein.

Introduction

In late 2003, our colleagues in the research group of Professor Philip Crews isolated a highly potent cytotoxic marine natural product from “an undescribed and inconspicuous sponge,

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Supporting Information Available: Synthetic procedures, complete spectroscopic data, ¹H and ¹³C NMR spectra for all new compounds, chiral HPLC data for **18** and **24** and CIF file for **22**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Psammocinia sp¹." The molecule, psymberin (assigned by Crews *et al.* as either **1** or **2**), was later determined to be identical to iriciniastatin A, a compound isolated and reported by Pettit and coworkers from extracts of *Ircinia ramose*.² The dual isolation of this compound from different sponges combined with the reported difficulty in isolating the compound from many sponge extracts adds evidence to the speculation that this molecule, along with structurally similar compounds, may in fact take origin from symbiotic bacteria.³ Over the past six years, a number of publications relating to the synthesis and semisynthesis of psymberin and analogs have been developed, including De Brabander's elegant first total synthesis of **1** and **2** in 2006, which conclusively determined that psymberin is in fact the 4*S* isomer **1**.^{4,5} To embark in the total synthesis of this remarkably active molecule, we endeavored to develop a rapid and convergent approach to both **1** and **2** as well as libraries of stereoisomer and structural analogs. Our successful efforts to produce several key building blocks are disclosed herein.

Results and Discussion

Our retrosynthetic analysis for **1** is depicted in Scheme 1. We envisioned a coupling of aryl fragment **3**, through a suitable organometallic agent, to an epoxide (not shown) to be built onto the lower portion of target fragment **6**, in which the C8 functionality is suitably protected. Subsequent manipulation of the C8 functionality to a variety of groups was deemed necessary to explore the often challenging formation of the stereochemically defined aminal functionality⁶ through coupling with fragments such as **4** or **5**. Thus, our strategy involved disconnecting the molecule into three main fragments, the aryl fragment **3**, the sidechain fragment as **4** or **5**, and the pyran core fragment **6**, which can be further deconstructed to **7**. In addition to allowing for a highly convergent assembly of **1**, the modularity of our approach would allow for alteration of stereochemistry and functionality on each of the three subunits so as to rapidly amass a library of analogs.

Excited to evaluate the potential for C8 diastereoiduction through several envisioned synthetic approaches, our initial goal was to obtain the advanced intermediate **7** as swiftly as possible. To this end, we relied heavily on the pioneering work of Kocienski and coworkers to synthesize the pyran core. Kocienski's synthesis of pederin, theopederin and the mycalamides all share the common pyran intermediate **8**.⁷ We envisioned that the analogous protected alcohol **9** (and later **10**) would dovetail nicely into our synthesis of **1**.

Our approach to compounds **9** (1st generation) and **10** (2nd generation) based on Kocienski's template are depicted in Schemes 2 and 3. The hopes of hastily moving multigram quantities of material through Kocienski's process were dashed on the discovery that our first generation substrate **9** suffered from a frustrating instability through many of the transformations. We attributed this decomposition to the loss of the primary *tert*-butyldimethylsilyl (TBDMS) ether, and thus repeated the synthesis of an analogous compound **10** that was truncated by one carbon and bore the more robust *tert*-butyldiphenylsilyl (TBDPS) protecting group at the primary alcohol.

The synthesis began with an asymmetric aldol reaction between silyl enol ether **13** and aldehyde **11** mediated by the oxazaborolidine **14**, generated *in situ* from *N*-tosyl valine and BH₃•THF.⁸ The enantiomeric ratio in this transformation was estimated to be 97:3 by ¹H NMR following conversion to the Mosher ester.⁹ While our initial yields were far lower than Kocienski's, optimization of the oxazaborolidine formation by increasing the reaction time increased the yield from 20% to 60%. A major challenge in this transformation was the isolation of two products from this transformation: the desired alcohol **17** as well as TMS-ether **15**. While treatment of **15** with mild acid could invoke the desired deprotection, it was at this step that we encountered what would be a recurring theme throughout the first generation synthesis: the surprising lability of the TBDMS ether. None of our attempts to remove the TMS ether were

successful without concomitant TBDMS loss, thus requiring a re-protection step to convert the diol to **17**. Incorporation of the more robust TBDPS protecting group eliminated the need for re-protection and gave **18** in a much higher 88% overall yield with comparable diastereoselectivity, determined to be 94:6 by chiral HPLC analysis.

With compounds **17** and **18** in hand, acetylation and Dieckmann condensation proceeded uneventfully to give β -keto lactones **21/22**. Recrystallization of both lactones to full enantioenrichment was possible at this stage and confirmed by optical rotation and chiral HPLC analysis. In addition, X-ray crystallographic analysis of an enriched sample of compound **22** gave a Flack parameter of 0.08, indicative of the desired absolute configuration.¹⁰ The three remaining steps involved methyl enol ether formation followed by DIBALH reduction to give enones **25** and **26**, which then underwent conjugate addition to give β -vinyl ketones **9** and **10**, respectively. At this stage, the difference in performance of the two compounds is quite striking: the overall yield of our second-generation substrate **10** (41%) is nearly double that of first generation substrate **9** (23%), and comparable to that for Kocienski's β -vinyl ketone **8** (38%). We attributed the lower comparative yields in the syntheses of **17** and **25** to the inability to perform the requisite acidic workup in each reaction without substantial loss of the TBDMS ether. The TBDMS group can be considered more vulnerable to deprotection under acidic conditions in part because of its decreased size relative to the TBDPS group, and also perhaps due to the increased distance from the bulkier region of the molecule that is imparted by the additional methylene on the pendant chain. However, the cause for the decreased yield in other transformations such as the conversion of **19** to **21** and the remarkable instability of **23** were less clear.

From this point on our synthesis diverges from Kocienski's template. The first desired transformation was an asymmetric ketone reduction on **9** or **10** to give the desired chirality at C11. We had hoped for substrate-induced diastereoselectivity in this transformation, but unfortunately we saw little selectivity with the use of common reducing agents such as LAH, DIBALH, NaBH₄, superhydride and Luche conditions. Fortunately, the first asymmetric reducing agent we employed, TarB-NO₂ in tandem with NaBH₄,¹¹ gave us the desired stereochemistry (confirmed by 1,3 diaxial NOE interactions among the pendant vinyl protons and those at C11 and C13 for compound **28**) at C11 with a 19:1 diastereomeric ratio for both the first- and second-generation substrates. This transformation was not as high-yielding as desired, however, due to a competing hydroboration reaction between the pendant alkene and the borane generated in the course of the reaction. Nonetheless, optimization of the dismal 10-33% yields to 55% on the second-generation substrate was eventually achieved. Silyl protection gave compounds **27** and **28**.

In anticipation of the impending coupling studies at the C8 center, the substrate was subjected to oxidative cleavage of the vinyl group to give aldehydes **29** and **7** (Scheme 4). The optimal yield for the second-generation product **7** was obtained by a two-stage, one-pot treatment with OsO₄/NMO followed by NaIO₄, in contrast to the lower-yielding first-generation procedure converting **27** to **29**, in which the intermediate 1,2 diol was isolated by chromatography prior to periodate cleavage. The relatively unstable aldehyde **7** could be easily protected as the dimethoxy acetal **6** for further manipulations at the lower portion of the molecule. However, installation of C16-C18 was deferred at this stage in favor of first performing model studies on the aminal formation reaction with the sidechain C1-N7 fragments.

In the early planning stages of our psymberin synthesis, the assembly of sidechain fragments, in both the natural and C4-epimer forms, were also synthetic sequences for which we had anticipated speedy completion. Our synthesis of the 4-*epi* sidechain **5** is depicted in Scheme 5. Beginning from known PMB ether **30** (obtained from (*S*)-glycidol) copper-catalyzed epoxide opening with isopropylidene Grignard reagent was followed by methylation to give methyl

ether **32**. Deprotection and oxidation gave aldehyde **33**. Compound **33** was then subjected to *syn*-selective cyanide induction using the method of Ward, *et al.* to afford cyanohydrin **34** in a 6:1 *syn:anti* diastereomeric ratio.¹² The unstable cyanohydrin was immediately protected and subjected to nitrile hydrolysis using Parkins and Ghaffar's catalyst¹³ giving separable amides **5** and **35**, which is enantiomeric to the desired "natural" sidechain.

With the 4-*epi* sidechain in hand, our initial inclination was to perform a similar route from (*R*)-glycidol to obtain the natural sidechain fragment *ent*-**35**, with an additional Mitsunobu-like inversion performed on the cyanohydrin formed from *ent*-**33** to afford the desired *anti* stereochemistry as seen in the natural product. This inversion is somewhat challenging due to the known tendency of aliphatic cyanohydrins to racemize under traditional Mitsunobu conditions.¹⁴ Unpublished experiments performed on similar compounds in our laboratory indicated this racemization can be avoided by employing a method similar to Effenberger and Stelzel,¹⁵ in which the cyanohydrin hydroxyl is first converted to a sulfonate leaving group and then displaced by an acetate to give the desired inversion of stereochemistry. While our studies indicated good success in this transformation using Shimizu's chlorinated mesylate as a leaving group,¹⁶ we ultimately determined that this approach to the natural sidechain was too lengthy and decided to focus our efforts on developing of a more efficient route to the completion of this small fragment.

Our more rapid pathway into the natural sidechain fragment focused on synthesizing the compound as the carboxylic acid **4**. In order to establish the requisite *anti* stereochemistry at C4-C5, we turned to MacMillan's elegant proline-catalyzed aldol reaction¹⁷ that has been shown to give bis-TPS ether **36** (Scheme 6) with a 9:1 diastereomeric ratio and a 93% *ee*.¹⁸ Immediate protection of this aldehyde gave alcohol **37**, which was fully resistant to methylation, presumably due to steric bulk about the secondary hydroxyl. Instead, selective deprotection of the primary silyl ether using HF-pyridine gave diol **38**.

From diol **38**, we first opted to convert the compound to the 1,2 cyclic sulfate ester **40**, which has been shown by Sharpless to readily accept various nucleophiles.¹⁹ Unfortunately, this compound reacted sluggishly in the presence of isopropylidene Grignard, and we struggled to ascertain appropriate conditions for the cleavage of the resultant sulfate ester to the desired free alcohol.²⁰

Fortunately, conversion of **38** to epoxide **42** using the method of Martinelli *et al.* proved far more fruitful (Scheme 7).²¹ Compound **42** was then opened and methylated to give **43** in good yield with the conditions we had employed in the synthesis of fragment **5**. Deprotection of the hemiacetal gives the aldehyde, which is ready for oxidation to either the acid **4** or other functionalities suitable for coupling with the pyran core.

While we were encountering unanticipated difficulties in the synthesis of the sidechain and pyran core fragments, our synthesis of our envisioned aryl fragment proceeded rapidly and in excellent yield. The construction of the desired compound **3** is depicted in Scheme 8, and began from known aldehyde **44**.²² Our initial attempts to perform the synthesis on the *bis*-silylated diphenol (not shown) were met with protection group loss and complex mixtures in the oxidation step. We thus opted for more robust acetate protecting groups, which were then converted to silyl ethers at the penultimate step. The phenols were then protected with acetyl chloride, giving **45** in 85% yield. Oxidation to the desired amide was first performed by treatment with *N*-hydroxysuccinimide followed by IBX to give activated ester **46**.²³ Interestingly, the high yield in this transformation was completely dependent on order of addition, requiring premixing of the substrate with NHS prior to oxidation (premixing of IBX with NHS prior to substrate addition gave yields varying from 25-50%). This is indicative that the actual mechanism of this transformation may differ from that reported in the literature,²⁴

which suggests that an intermediate IBX-NHS complex is the active oxidant. The activated ester was then treated with diethylamine to produce the desired aromatic amide with concomitant acyl hydrolysis, affording compound **47** in a 56% yield. The conversion to the desired TBDPS-protected product **3** could be achieved by two routes, which both proved to be similarly successful (84%) on a small scale.

Our initial unpublished results as well as personal communication with Professor De Brabander indicate the envisioned disconnection of this aryl fragment may suffer from the hydrolytic stability of the diethyl amide, which has thus far been entirely resistant to lactone closure outside of highly acidic refluxing conditions. Thus, some retooling of our dihydroisocoumarin synthesis is apparently necessary. This chemistry, as well as further elaboration of the pyran core and the preliminary results for our envisioned N7-C8 coupling scenarios are currently under investigation in our laboratory. These findings, combined with the eventual completion of the total synthesis of **1**, will be reported in due course.

Experimental Section

General Methods

All air and moisture sensitive reactions were carried out under an atmosphere of dry argon or nitrogen using oven-dried or flame-dried glassware and standard syringe techniques.

(2S,4R,6R)-4-(tert-butyldimethylsilyloxy)-6-[2-(tert-butylphenylsilyloxy)-ethyl]-5,5-dimethyltetrahydropyran-2-carbaldehyde (7)—Compound **28** (60 mg, 0.11 mmol, 1.0 equiv) was dissolved in a mixture of 5 mL *t*-BuOH, 1 mL THF and 0.5 mL water. *N*-methylmorpholine-*N*-oxide (28 mg, 0.24 mmol, 2.2 equiv) was added, followed by one drop of a 4% solution of OsO₄ in *t*-BuOH. The mixture was stirred overnight. The following day, pH 7.0 phosphate buffered saline (10 mL) was added followed by sodium periodate (128 mg, 0.6 mmol, 5.5 equiv). The mixture was stirred at room temperature for two hours and quenched with the addition of 500 mg solid Na₂S₂O₃. After stirring for 30 min, the solution was diluted with water and extracted with ethyl acetate. The combined organics were washed with saturated aqueous Na₂S₂O₃ followed by brine and dried over Na₂SO₄. Flash column chromatography (5% ethyl acetate in hexanes) gave 57 mg (95%) of aldehyde **7** as a colorless oil. $[\alpha]_D^{25} = +36.8$ (*c* 1.0, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ = 9.73 (d, *J* = 1.5 Hz, 1H), 7.70-7.65 (m, 4H), 7.45-7.37 (m, 6H), 4.12 (dd, *J* = 2.0, 6.5 Hz, 1H), 3.92 (dt, *J* = 5.0, 10.0 Hz, 1H), 3.83 (ddd, *J* = 3.5, 6.5, 10.0 Hz, 1H), 3.35 (dd, *J* = 1.5, 10.0 Hz, 1H), 3.22 (dd, *J* = 4.5, 11.0 Hz, 1H), 2.10 (ddd, *J* = 2.0, 4.5, 13.5 Hz, 1H), 1.81-1.72 (m, 2H), 1.63 (dddd, *J* = 5.0, 5.0, 10.0, 14.0 Hz, 1H), 1.05 (s, 9H), 0.90 (s, 9H), 0.84 (s, 3H), 0.81 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 205.8, 135.6, 133.9, 129.7, 127.7, 78.1, 72.7, 60.8, 38.7, 32.2, 29.3, 26.8, 25.7, 23.0, 19.1, 17.9, 12.7, -4.2, -5.2; IR (thin film) = 2958, 1735, 1472, 1258, 1112, 959, 837, 702 cm⁻¹; HRMS [M+H⁺] for C₃₂H₅₁O₄Si₂, calcd. 555.3320, found, 555.3337.

(2R,4R,6S)-4-(tert-butyldimethylsilyloxy)-2-[2-(tert-butylphenylsilyloxy)-ethyl]-6-dimethoxymethyl-3,3-dimethyltetrahydropyran (6)—Aldehyde **7** (44 mg, 0.08 mmol, 1.0 equiv) was dissolved in 2 mL trimethylorthoformate in an oven-dried flask under an atmosphere of nitrogen. Catalytic PTSA (1 mg) was added and the mixture was stirred at room temperature for 45 minutes. The reaction was quenched with the addition of 1 mL saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the combined organics were washed with brine, dried over Na₂SO₄, and filtered to give a crude oil that was subjected to flash column chromatography. Following purification, compound **6** (43 mg, 93%) was isolated as a clear, colorless oil. $[\alpha]_D^{26} = +19.8$ (*c* 1.2, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ = 7.71-7.67 (dt, *J* = 1.5, 8.0 Hz, 4H), 7.44-7.36 (m, 6H), 4.40 (d, *J* = 7.0 Hz, 1H), 3.84-3.75 (m, 3H), 3.54 (dd, *J* = 4.0, 8.0 Hz, 1H), 3.45 (dd, *J* = 2.0, 11.0 Hz, 1H),

3.36 (s, 3H), 3.22 (s, 3H), 1.95 (bs, 1H), 1.80–1.70 (m, 2H), 1.66 (ddd, $J = 5.5, 8.5, 13.5$ Hz, 1H), 1.06 (s, 9H), 0.92 (s, 3H), 0.91 (s, 9H), 0.84 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 135.6, 134.4, 134.2, 129.5, 127.6, 103.3, 73.1, 62.0, 54.8, 52.6, 38.1, 32.0, 30.1, 26.8, 25.7, 24.6, 19.1, 17.9, -4.4, -5.1$; IR (thin film) = 2956, 1471, 1256, 1091, 975, 835, 701 cm^{-1} ; HRMS $[\text{M}+\text{H}^+]$ for $\text{C}_{34}\text{H}_{57}\text{O}_5\text{Si}_2$, calcd. 601.3739, found, 601.37089.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Cichewicz RH, Valeriote FA, Crews P. *Org Lett* 2004;6:1951–1954. [PubMed: 15176791]
2. Pettit GR, Xu JP, Chapuis JC, Pettit RK, Tackett LP, Doubek DL, Hooper JNA, Schmidt JM. *J Med Chem* 2004;47:1149–1152. [PubMed: 14971894]
3. See Piel J. *Nat Prod Rep* 2009;26:338–362.362 [PubMed: 19240945] and the references therein.
4. For the total synthesis of **1**, see (a)Jiang X, García-Fortanet J, De Brabander JK. *J Am Chem Soc* 2005;127:11254–11255.11255 [PubMed: 16089449](b)Shangguan N, Kiren S, Williams LJ. *Org Lett* 2007;9:1093–1096.1096 [PubMed: 17319675](c)Huang X, Shao N, Palani A, Aslanian R, Buevich A. *Org Lett* 2007;9:2597–2600.2600 [PubMed: 17523653](d)Smith AB, Jurica JA, Walsh SP. *Org Lett* 2008;10:5625–5628.5628 [PubMed: 19072197]
5. For other articles related to the synthesis and stereochemical analysis of psymberin fragments and analogs, see (a)Kiren S, Williams LJ. *Org Lett* 2005;7:2905–2908.2908 [PubMed: 15987166](b)Green ME, Rech JC, Floreancig PE. *Org Lett* 2005;7:4117–4120.4120 [PubMed: 16146366](c)Rech JC, Floreancig PE. *Org Lett* 2005;7:5175–5178.5178 [PubMed: 16268531](d)249Henßen B, Kasparyan E, Marten G, Pietruszka J. *Heterocycles* 2007;74:245.(e)Huang X, Shao N, Palani A, Aslanian R, Buevich A, Seidel-Dugan C, Huryk R. *Tetrahedron Lett* 2008;49:3592–3595.3595(f)Jiang X, Williams N, De Brabander JK. *Org Lett* 2007;9:227–230.230 [PubMed: 17217271](g)Lachance H, Marion O, Hall DG. *Tetrahedron Lett* 2008;49:6061–6064.6064(h)Huang X, Shao N, Huryk R, Palani A, Aslanian R, Seidel-Dugan C. *Org Lett* 2009;11:867–870.870 [PubMed: 19199777]
6. For a recent example of successful entry into this challenging functionality via asymmetric catalysis, see Li G, Fronczek FR, Antilla JC. *J Am Chem Soc* 2008;130:12216–12217.12217 [PubMed: 18722443]
7. (a) Kocienski PJ, Narquizian R, Raubo P, Smith C, Boyle FT. *Synlett* 1998:1432–1434. (b) Kocienski P, Narquizian R, Raubo P, Smith C, Farrugia LJ, Muir K, Boyle FT. *J Chem Soc Perkin Trans* 2000;1:2357–2384.
8. (a) Kiyooka, Si; Kaneko, Y.; Kume, Ki. *Tetrahedron Lett* 1992;33:4927–4930. (b) Kiyooka, Si; Kira, H.; Hena, MA. *Tetrahedron Lett* 1996;37:2597–2600. (c) Kiyooka, Si; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J Org Chem* 1991;56:2276–2278.
9. Dale JA, Mosher HS. *J Am Chem Soc* 1973;95:512–519.
10. Flack HD, Bernardinelli G. *Acta Crystallogr, Sect A: Found Crystallogr* 1999;55:908–915.
11. (a) Suri JT, Vu T, Hernandez A, Congdon J, Singaram B. *Tetrahedron Lett* 2002;43:3649–3652. (b) Cordes DB, Nguyen TM, Kwong TJ, Suri JT, Luihrand RT, Singaram B. *Eur J Org Chem* 2005:5289–5285. (c) Kim J, Suri JT, Cordes DB, Singaram B. *Org Process Res Dev* 2006;10:949–958.
12. (a) Ward DE, Hrapchak MJ, Sales M. *Org Lett* 2000;2:57–60. [PubMed: 10814245] (b) Ward DE, Sales M, Hrapchak MJ. *Can J Chem* 2001;79:1775–1785.

13. Ghaffar T, Parkins AW. *Tetrahedron Lett* 1995;36:8657–8660.
14. Warmerdam EGJC, Brussee J, Kruse CG, van der Gen A. *Tetrahedron* 1993;49:1063–1070.
15. Effenberger F, Stelzer U. *Angew Chemie Int Ed Engl* 1991;30:873–874.
16. Shimizu T, Hiranuma S, Nakata T. *Tetrahedron Lett* 1996;37:6145–6148.
17. (a) Northrup AB, Mangion IK, Hettche F, MacMillan DWC. *Angew Chem Int Ed* 2004;43:2152–2154. (b) Northrup AB, MacMillan DWC. *Science* 2004;305:1752–1755. [PubMed: 15308765]
18. In our hands, the diastereomeric ratio for this transformation ranged from 6:1 to 8:1
19. Gao Y, Sharpless KB. *J Am Chem Soc* 1988;110:7538–7539.
20. Kim BM, Sharpless KB. *Tetrahedron Lett* 1989;30:655–658.
21. Martinelli MJ, Nayyar NK, Moher ED, Dhokte UP, Pawlak JM, Vaidyanathan R. *Org Lett* 1999;1:447–450.
22. Xie L, Takeuchi Y, Cosentino LM, Lee KH. *J Med Chem* 1999;42:2662–2672. [PubMed: 10411486]
23. Mazitschek R, Mülbaier M, Giannis A. *Angew Chem Int Ed* 2002;41:4059–4061.
24. Schulze A, Giannis A. *Adv Synth Catal* 2004;346:252–256.

8 **9** R = CH₂OTBDMS
10 R = OTBDPS**Figure 1.**

Kocienski's synthesis of compound **8** served as our template for rapid assembly of pyran core fragments **9** and **10**

Scheme 1.
Retrosynthetic Analysis for **1** and **2**

11, 15, 17 R = CH₂OTBDMS
12, 16, 18 R = OTBDPS

Scheme 2.

Valine-mediated asymmetric aldol reaction is more successful with aldehyde **12** than with **11**

Scheme 3.
Further advancement of the pyran core fragments

Scheme 4.

Completion of the synthesis of aldehydes **29** and **7**, for use in model studies for the coupling with **4/5**, or transformed to **6** for further functionalization of the pyran core (Scheme 1)

Scheme 5.
Synthesis of the 4-*epi* sidechain in amide form (**5**)

Scheme 6.

Attempts to synthesize the natural sidechain from MacMillan's aldehyde **36**

Scheme 7.
Completion of the natural sidechain from diol **38**

Scheme 8.
Rapid assembly of aryl fragment **3**