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# Toward the Total Synthesis of Variecolin

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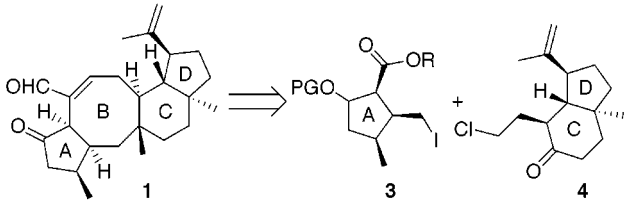
## ABSTRACT



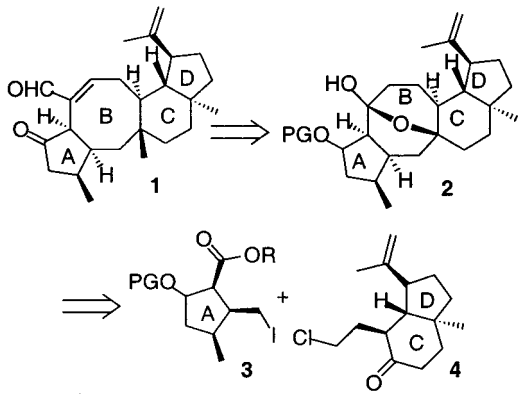

**An annulative approach toward the total synthesis of the sesterterpenoid variecolin (1) is presented. Synthesis of the key hemiketal, containing the core ABC ring skeleton, has been achieved on a model system by an expeditious route utilizing samarium(II) iodide. Furthermore, enantioselective syntheses of component fragments for the total synthesis have been developed.**

Herein we report progress toward the total synthesis of variecolin (**1**) using a modified samarium(II) iodide mediated annulation approach. We have demonstrated the feasibility of the formation of the core ABC carbocyclic skeleton on a model system and also report first-generation syntheses of the two components to be utilized in the total synthesis.

The sesterterpenoid variecolin (**1**) was first isolated by Hensens in 1991 and found to possess a number of interesting biological properties.[1] It is an antagonist of the angiotensin-II $AT_1$ receptor and more recently has been shown to be a potent immunosuppressant.[1,2] This immunosuppressant activity is of notable interest because of the simplicity of **1** in comparison to other immunosuppressants such as FK-506 and cyclosporin. Despite such interesting properties, variecolin has received little synthetic attention,[3] and so was an attractive target for total synthesis. Furthermore, at the outset of our studies the absolute configuration of variecolin had not been unambiguously determined and so an enantioselective synthesis would also provide a definitive structural determination.

Formation of the eight-membered ring hemiketal **2** was to be accomplished by a sequenced reaction of an iodo ester, **3**, and chloro ketone, **4**, mediated by $SmI_2$ (Scheme 1). We previously reported this approach to medium sized carbocycles on simplified systems, and it was hoped that a similar strategy could be used to construct **2**.[4] Nevertheless, the use of an annulation to construct an elaborate carbon skeleton was not without risk.

**Scheme 1**




(1) Hensens, O. D.; Zink, D.; Williamson, J.; Lotti, V. J.; Chang, R. S. L.; Goetz, M. A. *J. Org. Chem.* **1991**, *56*, 3399−3403.
(2) Fujimoto, H.; Nakamura, E.; Okuyama, E.; Ishibashi, M. *Chem. Pharm. Bull.* **2000**, *48*, 1436−1441.
(3) Piers, E.; Boulet, S. L. *Tetrahedron Lett.* **1997**, *38*, 8815−8818.
(4) (a) Molander, G. A.; Alonso-Alija, C. J. *J. Org. Chem.* **1998**, *63*, 4366−4373. (b) Molander, G. A.; Machrouhi, F. *J. Org. Chem.* **1999**, *64*, 4119−4123 and references therein.

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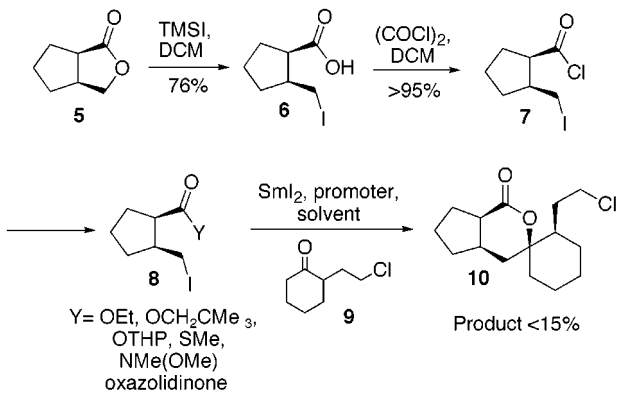
During the preparation of this Letter, Fujimoto and coworkers demonstrated that the absolute configuration of variecolin was, in fact, **1**. This is the enantiomer of the originally reported structure.[2] Unfortunately, the synthetic work carried out in our laboratory to that point was based on the original assignment which was founded upon biosynthetic considerations. However, the approach described herein retains its validity because both enantiomers of **3** and **4** are readily available by making simple adaptations in the synthetic schemes.

**Model Studies.** A racemic model system was first utilized to investigate the feasibility of the coupling step. We hoped lactone **5** would be a suitable precursor to the iodo ester model for **3** and that **9** would serve as a surrogate for the chloro ketone **4**.[4,5] After significant experimentation it was found, much to our frustration, that the *cis* geometry of all iodo carboxylic acid derivatives **8** prevented the expected $SmI_2$-promoted sequenced reaction from occurring under all conditions attempted (Scheme 2). Presumably, formation of

**Scheme 2**

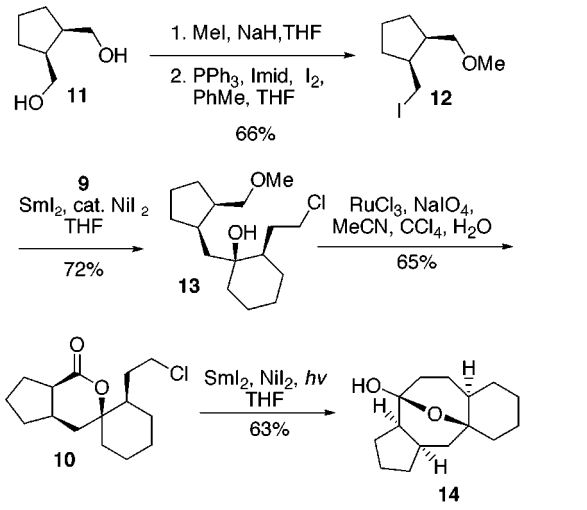



a *cis*-fused cyclobutanone occurs, leading to a complex mixture of degradation products.

Therefore, a stepwise approach was investigated wherein the carbonyl group of the iodo ester was replaced by a protected alcohol. Hence, reduction of the racemic lactone **5** with $LiAlH_4$ gave the diol **11** in 92% yield. In attempted transformations to the desired halide, the sterically demanding *cis* geometry prevented the use of large ether protecting groups such as TBDMS because iodination of the remaining free alcohol failed. Synthesis of the seemingly unattractive methyl ether and subsequent iodination of this material gave **12** in 66% yield over two steps (Scheme 3). Coupling of **12** with the chloro ketone **9** proceeded in 72% yield to give racemic **13** as a 1:1 mixture of diastereomers owing to the use of racemic components.[6]

Sharpless had reported oxidation of methyl ethers to the corresponding methyl esters using catalytic ruthenium tetroxide generated in situ from sodium periodate and ruthenium chloride.[7] Use of this protocol would avoid tedious deprotection and oxidation of the alcohol. To our delight, oxidation of **13** indeed furnished the lactone **10** *directly* in 65% yield.

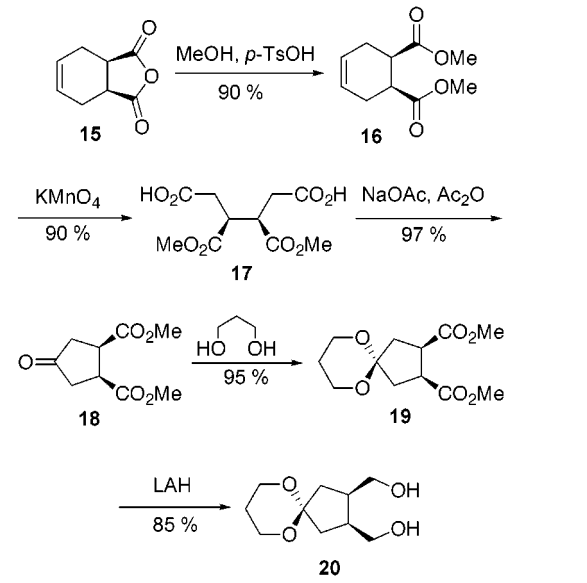
**Scheme 3**




Finally, cyclization of **10** with $SmI_2$ under photochemical conditions yielded the desired hemiketal **14** in 63% yield (Scheme 3). With the successful synthesis of racemic hemiketal **14** achieved, enantioselective syntheses of lactone **29** (precursor to the iodo ether) and chloro ketone *ent*-**4** were investigated.

**Synthesis of Enantiopure Lactone 29.** The commercially available and inexpensive tetrahydrophthalic anhydride **15** was converted into the diester **16** (Scheme 4). Subsequent oxidation of the double bond furnished **17**.[8] Cyclization and decarboxylation of **17** to **18** followed by protection under standard conditions yielded the 1,3-dioxane **19** in 95% yield.

**Scheme 4**




(5) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817−824.

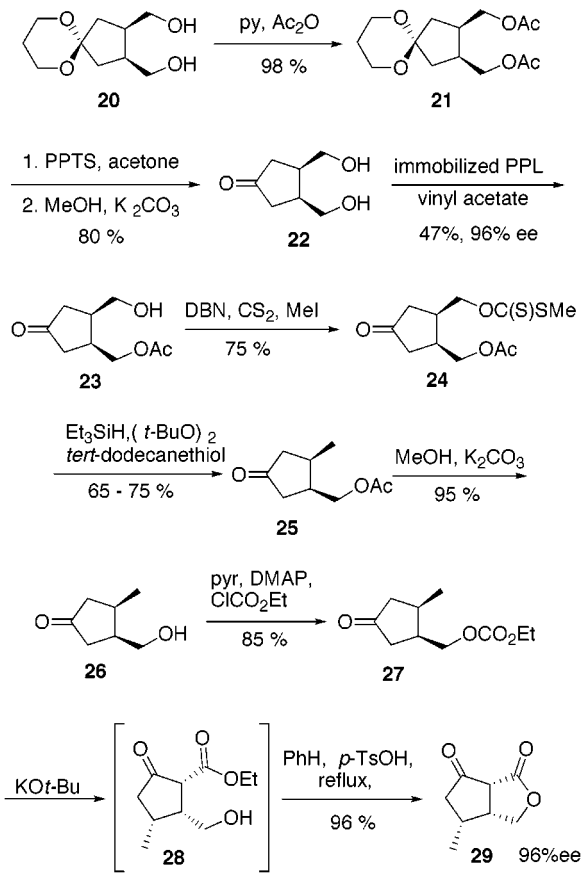
(6) Previous studies demonstrated that addition to the ketone is always *trans* to the adjacent alkyl chloride chain. See ref 4.

It was found that reduction of **19** to the diol **20** was best achieved using $LiAlH_4$.[9]

The enantiospecific introduction of the acyl unit (which serves as a temporary protecting group) to give ultimately **23** can be envisaged to occur in a number of ways. Either asymmetric hydrolysis and deprotection of the diacetate **21** or asymmetric acylation of **22** would afford the correct enantiomer **23**. Gais, in fact, had shown that porcine pancreas lipase (PPL) could be used for either asymmetric hydrolysis or asymmetric acylation on substrates similar to **21** and **22** by choice of suitable conditions.[10]

Reaction of crude PPL enzyme (immobilized on Kieselgur) with **22** utilizing vinyl acetate as the acylating agent and solvent gave **23** in 47% yield and 96% ee (Scheme 5).[11] The

**Scheme 5**

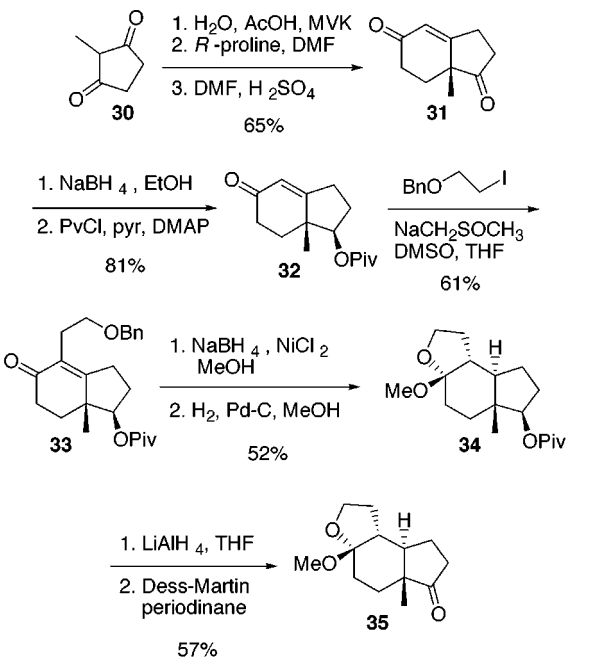



enantioselectivity was verified by chiral GC. Clearly, the free hydroxyl group of **23** can be orthogonally protected and the acetyl group removed to furnish the enantiomer required for the synthesis of **3**.

Conversion of **23** to the xanthate ester **24** under standard conditions occurred with no observable racemization as verified by chiral HPLC. Reduction of the xanthate group of **24** afforded **25** in 65−75% yield. Cleavage of the acetyl group of **25** with $K_2CO_3$ in methanol and conversion of the resultant hydroxyl group to the carbonate **27** proceeded without difficulty. Finally, carbonate **27** was treated with KO*t*-Bu and afforded, after heating at reflux in the presence of *p*-TsOH, enantiomerically enriched keto lactone **29** (Scheme 5).

**Synthesis of Chloro Ketone *ent*-4.** We selected as starting material for the synthesis of chloro ketone *ent*-**4** the enantiomerically pure Hajos−Parrish ketone **31**. The preparation of this compound has been carefully described in the literature.[12] The enantiomer of **31** is easily available using the less expensive (*S*)-proline. Reduction of dione **31** to the alcohol under modified literature conditions and protection of the crude alcohol as the pivaloyl ester furnished **32** in 81% yield (Scheme 6).[13]

**Scheme 6**




Alkylation of indanone **32** using published procedures was not straightforward. The desired product **33** was obtained in only 31% yield.[14] To our delight, however, use of a mixture of THF and DMSO as solvent in the initial step gave **33** in 61% yield.

Reduction of the alkylated indanone **33** ($NaBH_4/NiCl_2$) gave the unstable *trans*-fused ketone in a modest 49% yield.[15]

(7) Gais, H. J.; Bülow, G.; Zatorski, A.; Jentsch, M.; Maidonis, P.; Hemmerle, H. *J. Org. Chem.* **1989**, *54*, 5115−5122.

(8) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(9) Cope, A. C.; Herrick, E. C. *J. Am. Chem. Soc.* **1950**, *72*, 983−987.

(10) (a) Gais, H.-J.; Hemmerle, H. *Tetrahedron Lett.* **1987**, *28*, 3471−3474. (b) Gais, H.-J.; Hemmerle, H.; Kossek, S. *Synthesis* **1992**, 169−173. (c) Hemmerle, H. Ph.D. Dissertation, Universität Freiburg, 1990.

(11) Unreacted starting material and diacylated material were recycled easily to improve the overall conversion to **23**.

(12) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1984**, *63*, 26−36.

(13) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Scimanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675−681.

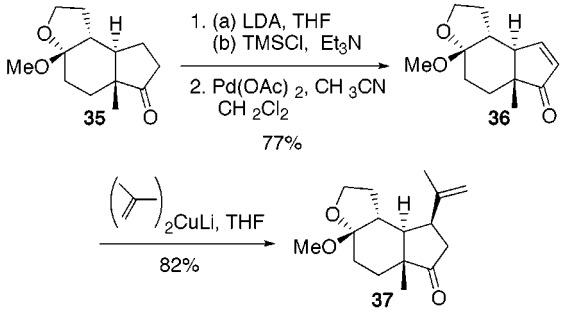
(14) (a) Ihara, M.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1990**, *55*, 4497−4498. (b) Sugimura, T.; Paquette, L. A. *J. Am. Chem. Soc.* **1987**, *109*, 3017−3024.

Subjection of the *trans*-fused ketone to traditional hydrogenolysis conditions yielded the ketal **34**. Direct hydrogenation, avoiding isolation of the sensitive intermediate ketone, led to an increased yield of 52% over the two steps.

Removal of the pivaloate ester of **34** with $LiAlH_4$ furnished the desired unprotected alcohol. Oxidation of the secondary alcohol was most successfully achieved by employing Dess−Martin conditions to furnish **35** in 57% yield from **34**.[16] Confirmation of the structure of **35** was achieved by X-ray analysis.

α,β-Unsaturation was introduced following a two-step procedure that gave **36** in 77% yield (Scheme 7).[17] We

**Scheme 7**



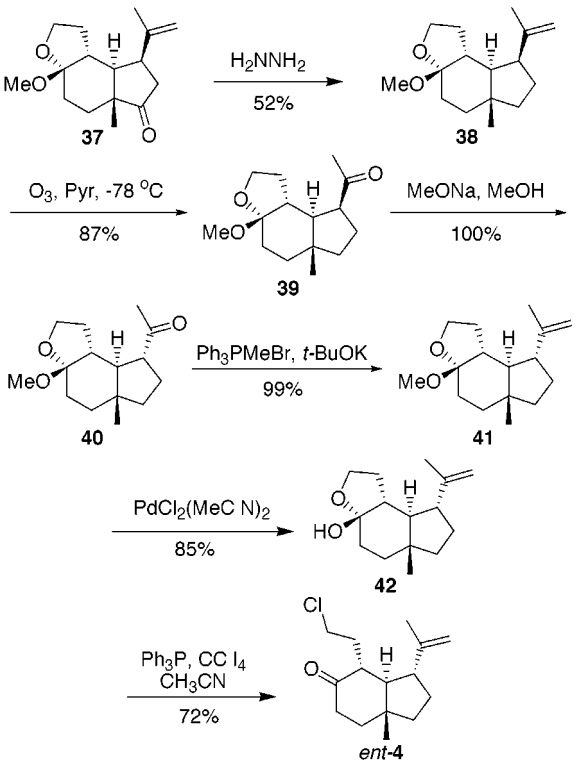

planned to introduce the desired isopropenyl group of the natural product by means of an organocuprate Michael addition. On the basis of a previous report on a similar system, we expected the axial methyl of the fused bicyclic system to effectively block the *pro-S* face of the α,β-unsaturated ketone.[3] Ketone **37** was obtained in 82% yield as a single diastereomer. However, X-ray analysis showed the isopropenyl group to be *cis* to the methyl substituent on the cyclopentanone ring.

To correct the configuration of the isopropenyl group, we decided to oxidize the double bond to a methyl ketone and epimerize it. A quick computational study (MacSpartan Pro, AM1) showed the desired isomer (8*R*)-**40** to be 1.6 kcal/mol more stable than its epimer (8*S*)-**39**.

Reduction of ketone **37** proved troublesome. The procedure described by Schmuff and Trost afforded **38** in a moderate 52% yield (Scheme 8).[18] Ozonolysis of **38** provided ketone **39** in 87% yield. To our delight, epimerization of (8*S*)-**39** with a catalytic amount of sodium methoxide in methanol afforded ketone (8*R*)-**40** in quantitative yield. Wittig reaction to reinstall the double bond afforded ketal **41** in 99% yield.

Deprotection of the ketal **41** to the corresponding hemiketal **42** with catalytic amounts of $PdCl_2(MeCN)_2$ in a mixture of $CH_3CN$ and $H_2O$ occurred in 85% yield.[19] The structure of

**Scheme 8**




**42** having the correct stereochemistry on all stereogenic centers was confirmed by X-ray. Finally, treatment of **42** with $Ph_3P$ and $CCl_4$, in $CH_3CN$ afforded chloro ketone *ent*-**4** in 72% yield, along with 22% of unreacted starting material.[20]

To conclude, we have developed an approach to the synthesis of variecolin via a modified annulation procedure. Efforts are underway to synthesize the correct enantiomers of each component fragment, and more efficient second-generation syntheses of these fragments along with improved methods to couple them are being investigated.

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**Supporting Information Available:** Experimental procedures and characterization of all novel compounds and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Khurana, J. M.; Gogia, A. *Org. Prep. Proced. Int.* **1997,** *29*, 1−32.
(16) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *49*, 4155−4156. (b) Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710−714.
(17) Krafft, M. E.; Dasse, O. A.; Fu, Z. *J. Org. Chem.* **1999**, *64*, 2475−2485.
(18) Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404−1412
(19) (a) Kharasch, M. S.; Seyler, R. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882−884. (b) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705−708. (c) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183−5187
(20) Appeal, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811.