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Total Synthesis of (−)-Apicularen A

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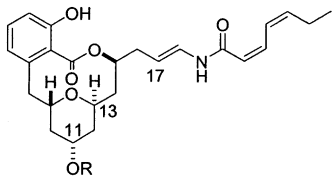
Abstract: Complete details of an asymmetric synthesis of apicularen (**1**) are described. The synthesis has been accomplished using a highly diastereo- and enantioselective [4 + 2] annulation for the assembly of the functionalized pyran core. An underdeveloped lactonization method involving an NaH promoted transesterification of an advanced intermediate bearing an aryl cyanomethyl ester was used for the macrolactonization step.

Introduction

Apicularen A, **1**, was identified by Jansen and co-workers during a screening of the myxobacterial genus for biologically active metabolites.[1] During this process, it was determined that nearly all strains from the genus *Chondromyces* produced this common highly cytotoxic metabolite. This compound is a powerful inhibitor of human cancer cells, including the multidrug-resistant line KB-VI.[2] In addition, the effects of apicularen A on in vivo angiogenesis of bovine aortic endothelial cells (BAECs) were investigated by Kwon and co-workers. It was found that apicularen A exhibited potent and inhibitory effect on the growth of BAECs without any evidence of cytotoxicity even when concentrations were increased to 10 ng/mL. This agent also showed inhibition of basic fibroblast growth factor (bFGF)-induced invasion and capillary tube formation of BAECs at low concentration. Accordingly, apicularen A represents a novel antiangiogenic compound with potent antitumor activity.[3] Structurally, this compound features a *trans*-hydroxypyran with a salicylic acid residue within a 10-membered lactone, which bears a highly unsaturated enamide side chain. This natural product is usually found with varying amounts of its glycoconjugate with *N*-acetyl glucose, known as apicularen B. Biosynthetic studies showed that they are acetate-derived polyketides containing a glycine residue as a precursor of an enamide side chain. Herein we report a total synthesis of apicularen A using an enantioselective [4 + 2] dihydropyran annulation to assemble the core of the natural product.[4]

Results and Discussion

Retrosynthesis of Apicularen A. Scheme 1 outlines our retrosynthetic strategy for apicularen A where the first bond disconnection relied on a vinylic substitution between vinyl iodide **2** and unsaturated amide side chain **3**.[5] Further disconnection of the macrolide revealed the hydroxy-ester **4**. We reasoned this intermediate could be obtained from an asymmetric allylation of aldehyde **5**.[6] This material was derived from dihydropyran **6a**, which was envisioned to result from a [4 + 2] annulation of the illustrated chiral allylsilane **7a** and salicylate-aldehyde **8a**.[7]



Apicularen A, **1**, R = H;
Apicularen B, R = *N*-acetyl-β-glucosamine.

Figure 1.

Synthesis of Dihydropyran through [4 + 2] Annulation. When we initiated a study concerning [4 + 2] annulation between chiral allylsilanes **7** and aldehydes, we chose phenylacetaldehyde as one of the reaction partners because of its loose structural resemblance to the salicylate moiety of apicularen A. We soon learned that the organosilanes used in this study exhibited a turnover in the stereochemical course of the annulation from our earlier studies with related crotylsilanes; for instance, where a *cis*-pyran was assembled from a *syn*-crotylsilane **7d**,[7a] a *cis*-pyran resulted from an anti diastereomer of

(1) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.
(2) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913.
(3) Kwon, J. H.; Kim, D. H.; Shim, J. S.; Ahn, J. W. *J. Microbiol. Biotechnol.* **2002**, *12*, 702.
(4) For previous total syntheses of apicularen A, see: (a) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217. (b) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701. For studies toward syntheses of apicularen A, see: (c) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069. (d) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549. (e) Kuhnert, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643. (f) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104. (g) Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357.
(5) For preparation of amide side chain, **3**, see: (a) Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645. (b) Fürstner, A.; Dierske, T.; Thiel, O.; Blanda, G. *Chem.—Eur. J.* **2001**, *7*, 5286. (c) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407.
(6) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.
(7) For related annulations, see: (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836. (b) Huang, H.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991. (c) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, *SI*, 955.

Scheme 1. Retrosynthesis of Apicularen A

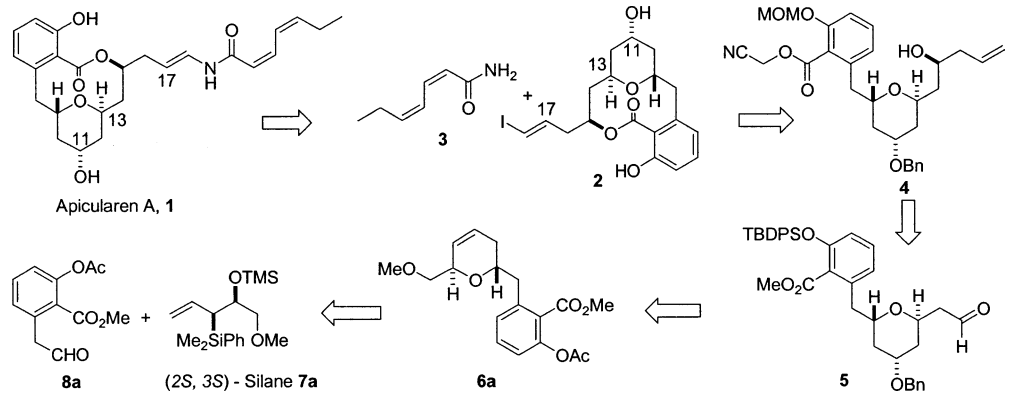
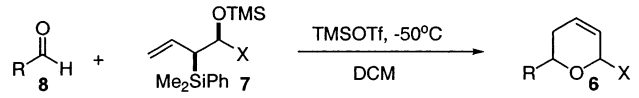


Table 1. Synthesis of Dihydropyran via the [4 + 2] Annulation



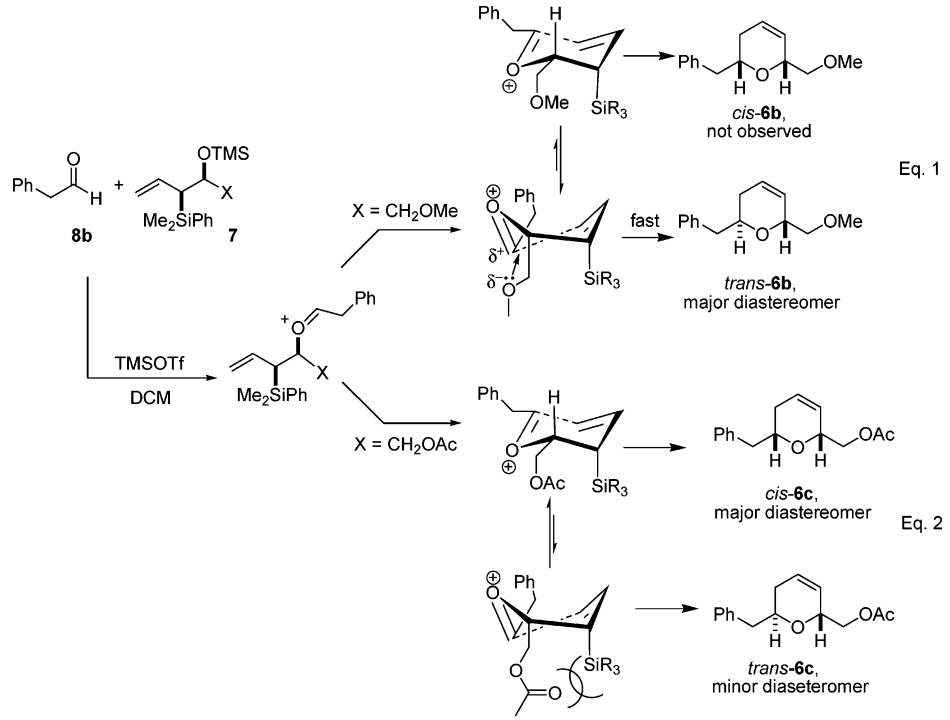
entry	Aldehyde	Allyl silane	major isomer[a]	yield (%)[b]	dr (trans:cis)[c]
1	8b	7a	6b	91	> 30:1
2	8b	7b	6c	54	1 : 3
3	8b	(*rac*)-7c	(*rac*)-6d	60	1 : 1
4	8c	(*rac*)-7c	(*rac*)-6e	85	1 : 12
5	8d	(*rac*)-7c	(*rac*)-6f	87	<1 : 30

[a] Stereochemistry of the pyrans was assigned by NOE experiments. [b] Yields were based on pure materials isolated by chromatography on SiO_2. [c] The product ratios were determined by ^1H NMR (400 MHz).

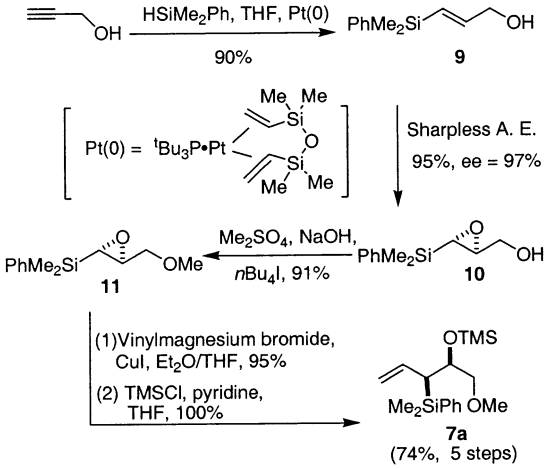
allylsilane **7b**. In the course of the development of our annulation, Roush and co-workers reported the synthesis of *cis*-2,6-disubstituded dihydropyrans using allylsilanes derived from an asymmetric γ-silyl allylboration of aldehydes. In that report, a similar turnover in the diastereoselectivity was observed for the annulation between aldehydes and allylsilanes that possessed an anti stereochemical relationship.[7c] We learned that the stereochemical course of the annulation was determined by relative stereochemical arrangement (syn or anti) of the silicon and adjacent silyl ether (OTMS) of the crotylsilane.[7a] Thus, in our initial studies we investigated the reaction between phenylacetaldehyde and *syn*-allylsilane **7**, the results of which are summarized in Table 1. To our surprise, the diastereoselectivity of annulation was dependent on the type of the functional group X associated with the organosilanes (Table 1). We have observed that the functional group X directly affected the sense and magnitude of diastereoselectivity. For instance, silane **7a** (X = CH_2OMe, entry 1, Table 1) produced a pyran with an excellent level of diastereoslectivity, and only a trans diastereomer was detected in the reaction crude mixture; whereas silane **7c** (X = CO_2Me, entry 3, Table 1) was unselective. The stereochemical outcome of the annulation between aldehyde **8b** and silane **7b** (X = CH_2OAc, entry 2, Table 1) resulted in the formation of a *cis*-pyran as the major isomer. Our mechanistic interpretation for the reversal of the stereochemical course of the annulation is illustrated in Scheme 2. To achieve an effective $\sigma-$p orbital overlap for stabilization of the developing β-carbocation in the ring formation process, we have positioned the silicon group in a pseudoaxial orientation in a twist boatlike transition state and an axial orientation in a chairlike transition state.[8] Formation of the *trans*-dihydropyran from the reaction between silane **7a** and aldehyde **8b** may proceed through a twist boatlike transition state. It is possible that electrostatic attraction between the nonbonding lone pair of electrons of methyl ether and the positively charged oxocarbenium, which resides on the carbon atom, stabilizes the twist boat conformer and accelerates the annulation as illustrated in eq 1 (Scheme 2).[9] The complimentary *cis*-dihydropyran derived from the reaction of silane **7b** and aldehyde **8b** may proceed through a chairlike transition

(8) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677.
(9) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521 and references therein.

Scheme 2. Possible Transition States for [4 + 2] Annulation



Scheme 3. Synthesis of Allyl Silanes



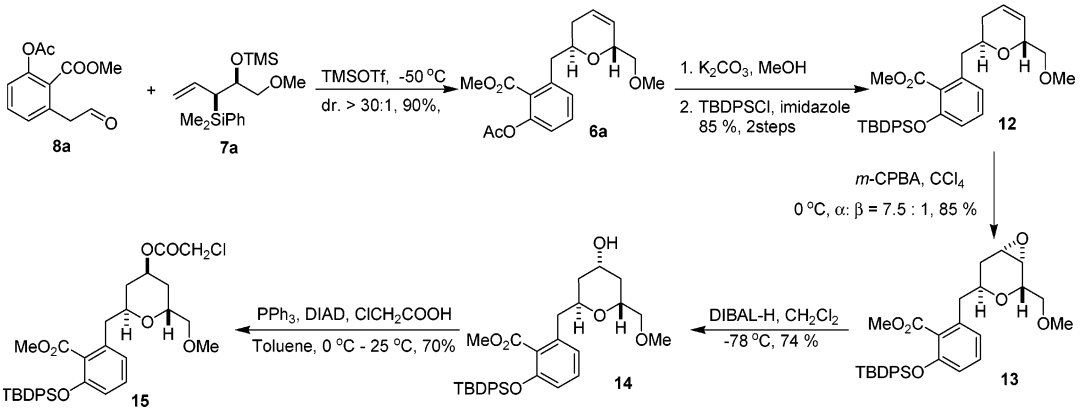
state shown in eq 2. The electron density at the oxygen atom may be decreased by the electron withdrawing acetate group (Ac) in **7b** that leads to a decrease of the electrostatic effect. The chair conformer is favored under this circumstance considering the steric destabilizing interaction between X (X = CH_2-OAc) and bulky silyl group ($SiMe_2Ph$) in twist boat conformer. The turnover of the sense of diastereoselectivity resulting from the subtle structural changes of silane reagents (**7a**, X = CH_2-OCH_3 → **7b**, X = CH_2OAc) underscored the unique reactivity and selectivity profile of these chiral organosilanes and is currently under further investigation. In addition, when conjugated aldehydes were employed, only allylsilane **7c** (X = CO_2-Me) gave high levels of diastereoselectivity to produce a *cis*-pyrans (entries 4 and 5, Table 1). Once assured that allylsilane **7a** consistently provided a *trans*-pyran, we evaluated the scope of the reaction using a range of aldehydes. We have showed that the annulation between allylsilane **7a** and aliphatic aldehydes proceeded smoothly to produce a *trans*-dihydropyran (Table 2). Importantly, the functionalized aldehyde **8a** intended for the apicularen synthesis also gave the desired pyran in high yield and diastereoselectivity (entry 1, Table 2).

Synthesis of Allylsilane. To access useful quantities of enantiomerically enriched allylsilane **7a**, an efficient synthesis was developed using a modification of Chong's protocol (Scheme 3).[10] The allylic alcohol **9** was obtained via a platinum catalyzed regioselective hydrosilation.[11] This material was subjected to a Sharpless epoxidation to produce highly enantiomerically enriched epoxy alcohol **10** (ee = 97%).[12] After protection of free alcohol as its methyl ether, the epoxide **11** underwent a regioselective ring opening with vinylmagnesium bromide and a catalytic amount of CuI providing a chiral allylsilane in an excellent yield and as a single regioisomer. Not surprisingly, the protection of primary alcohol was crucial to the success of this reaction as it shut down the undesired Peterson elimination pathway (Peterson olefination).[13] The desired chiral allylsilane **7a** was obtained in quantitative yield after silylation of the secondary alcohol. This silane was made available in useful quantities (>15 g) using an efficient five-step sequence with an overall yield of 74%.

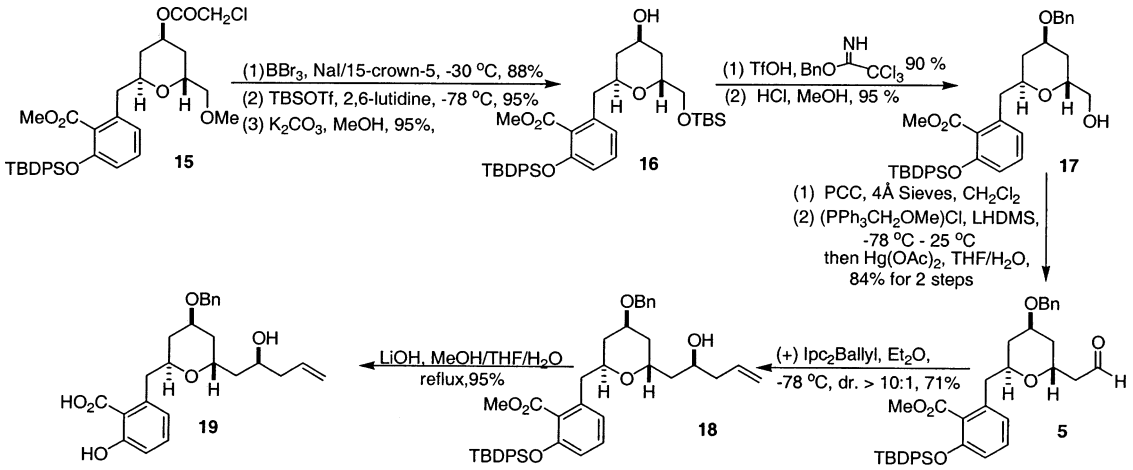
Synthesis of the Macrolide of Apicularen A. With a reliable route to useful quantities of the required allylsilane in hand, we began the synthesis of apicularen A with the annulation between aldehyde **8a** and chiral organosilane **7a**. Gratifyingly, the first step of our route proceeded smoothly in the presence of TMSOTf to afford desired dihydropyran **6a** in excellent yield and as a single diastereoisomer (Scheme 4). Methanolysis of the phenolic acetate followed by protection of the free phenol as a silyl ether with TBDPSCl gave dihydropyran **12**. The

(10) Chauret, D. C.; Chong, J. M.; Ye, Q. *Tetrahedron: Asymmetry* **1999**, *10*, 3601.
(11) Beresis, R. T.; Solomon, J. S.; Yang, M.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78.
(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(13) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

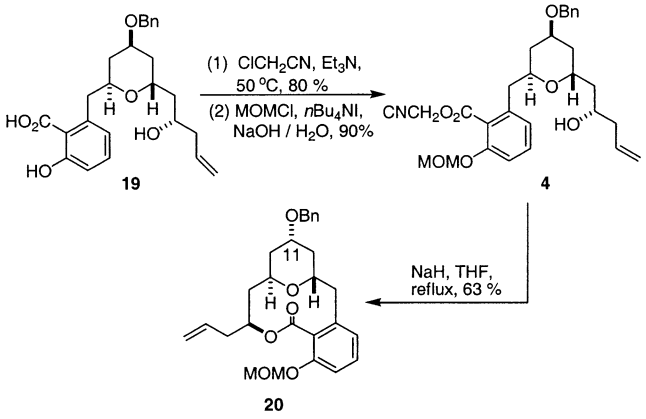
Scheme 4



Scheme 5



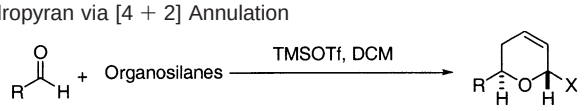
Scheme 6

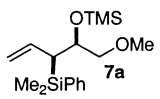
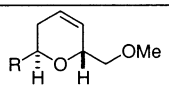
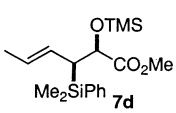
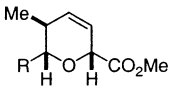


attempts to install an 11-hydroxy group by oxymercuration[14] or hydroboration[15] gave a complex mixture of regio- and diastereoisomers. Therefore, the dihydropyran **12** was subjected to *m*-CPBA epoxidation (CCl_4, 0 °C), and a useful diastereoselectivity was achieved (α:β = 7.5:1).[16] Regioselective epoxide opening by DIBAL-H reduction was realized at −78 °C without involvement of the aryl ester to give hydroxy pyran **14**.[17] The configuration of the newly installed 11-hydroxy group turned out to be opposite to the one of apicularen A indicating that the epoxidation reaction gave the wrong diastereomer as the major product. Accordingly, a Mitsunobu reaction was used to invert the resulting secondary alcohol and install the correct stereochemistry.[18] The primary methyl ether **15** was selectively cleaved with BBr_3/NaI/15-crown-5 at −35 °C (Scheme 5).[19] Protection of primary alcohol as a TBS silyl ether was followed by methanolysis of the chloroacetate. The resulting secondary alcohol was reprotected as a base-stable benzyl ether **16**.[20] Acidic cleavage of primary TBS ether afforded alcohol **17**, which was subsequently oxidized to an aldehyde with PCC in the presence of molecular sieves in CH_2Cl_2.[21] The resulting aldehyde was homologated using a phosphorus-based olefination with methoxymethylene triphenylphosphine.[22] Hydrolysis of the enol ether mediated by $Hg(OAc)_2$ provided the homologated aldehyde **5** in high yield. This material was treated with (+)-Ipc_2Ballyl furnishing the desired advanced intermediate **18** in 71% yield (dr = 12:1).[23] Hydrolysis of this material using LiOH in a solution of MeOH/THF/H_2O (1:4:1) at reflux delivered hydroxy acid **19**. Unfortunately, attempts to directly lactonize the resulting hydroxy acid **19** failed. We reasoned that the acidity of the free phenol could be problematic for lactonization protocols employing carboxylate activation meth-

(14) Brown, H. C.; Geoghegan, P., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522.
(15) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 247.
(16) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693.
(17) Hayakawa, H.; Iida, K.; Miyazawa, M.; Miyashita, M. *Chem. Lett.* **1999**, 601.
(18) (a) Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317. (b) Mitsunobu, O. *Synthesis* **1981**, 1.
(19) Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* **1981**, *22*, 4239.
(20) Iversen, T.; Bundle, K. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.
(21) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.
(22) Maercker, A. *Org. React.* **1965**, *14*, 270.
(23) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

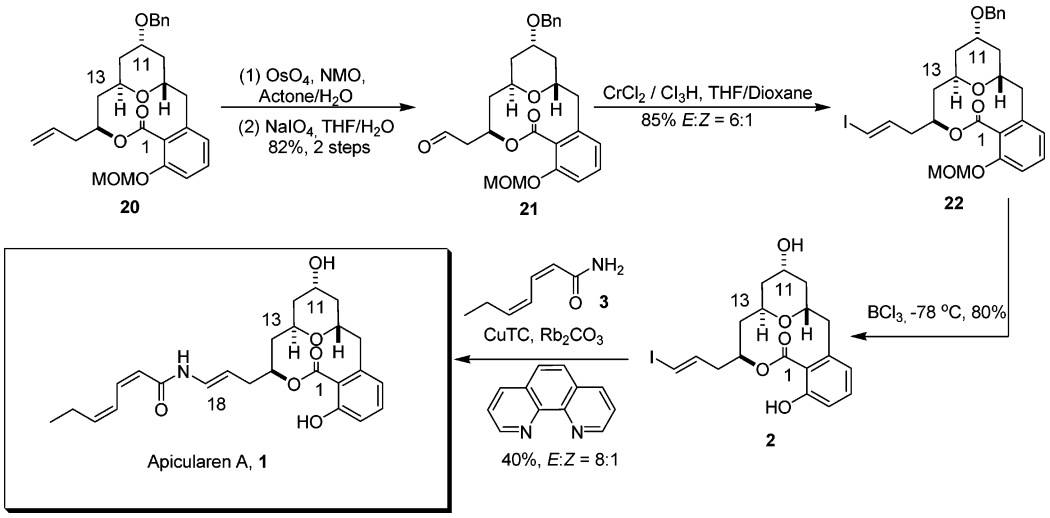
Table 2. Construction of *trans*-Dihydropyran via [4 + 2] Annulation



entry	Aldehyde	silane	major isomer[a]	yield (%)[b]	dr (trans:cis)[c]
					
1	**8a**	**7a**	*trans*, **6a**	90	>30:1
2	*i*PrCHO	**7a**	*trans*, **6g**	91	>30:1
3	*c*-HexCHO	**7a**	*trans*, **6h**	95	10:1
4	$PhCH_2CHO$	**7a**	*trans*, **6b**	91	>30:1
					
5[d]	*i*PrCHO	**7d**	*cis*	86	1:9
6[d]	*c*-HexCHO	**7d**	*cis*	85	1:15

[a] The stereochemistry of the pyran products was assigned by NOE measurements. [b] Yields were based on pure materials isolated by chromatography on SiO_2. [c] The product ratio was determined by ^1H NMR (400 MHz). [d] See ref 7a.

Scheme 7



ods. In that regard, we sought a viable solution that would efficiently lead to the formation of the macrolide. Recently, Porco, Shen, and Lin have used a salicylic cyanomethyl ester moiety for an efficient intermolecular transesterification.[24] In the present case, this ester was selectively installed using the chloroacetonitrile in the presence of Et_3N at 50 °C (Scheme 6).[25] Selective protection of the free phenol as a MOM ether was achieved using MOMCl in aqueous NaOH solution.[26] The crucial lactonization of cyanomethyl ester **4** was accomplished using a NaH promoted transesterification in a dilute solution of refluxing THF affording macrolide **20** in good chemical yield.

Completion of the Synthesis of Apicularen A. With the apicularen macrolide core **20** in hand, we were positioned for introduction of the enamide side chain and completion of the synthesis. Two-step oxidative cleavage of terminal olefin provided an unstable aldehyde **21** (Scheme 7). The crude material was used without purification in the Takai iodoolefination providing *E*-vinyl iodide **22** (*E*:*Z* = 6:1) in mixed solvents of THF and dioxane.[27] Complete deprotection of this advanced intermediate was achieved using BCl_3 at −78 °C. In the final stage, the CuTC catalyzed substitution of vinyl iodide **2** with unsaturated amide **3** proceeds to yield apicularen A, **1** (*E*:*Z* = 8:1), in 40% yield at 58 °C under conditions described by Porco and Shen.[28] In our case, the diamine ligand and reaction temperature were crucial to the success of the reaction and completing the synthesis of the natural product. No diamine ligand resulted in no product and decomposition of vinyl iodide.

(24) For base-induced intermolecular transesterification reaction of cyanomethyl ester, see: (a) Scherlock, M. H. S. *African Pat*. ZA 6802187, CAN 70, 106224. (b) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.

(25) Hugel, H. M.; Bhaskar, K. V.; Longmore, R. W. *Synth. Commun*. **1992**, *22*, 693.

(26) For selectively protecting phenol, see: Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522.

(27) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. For an optimization of the solvent system for Takai olefination reaction, see: Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

(28) (a) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (b) Shen, R.; Lin, C.; Bowman, E.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc*. **2003**, *125*, 7889.

And, high temperature (80 °C) resulted in olefin at C17 position as a 1:1 *E*/*Z* mixture. The chromatographic and spectroscopic data of synthetic **1** are fully consistent with those of an authentic sample.[1]

Conclusion

We have completed the total synthesis of apicularen A. A key feature of this synthesis included highly enantio- and diastereoselective construction of *trans*-2,6-disubstituted dihydropyran via a [4 + 2] annulation between a functionalized phenylacetaldehyde and *syn*-allylsilane **7a**. Also we detailed the underdeveloped base-promoted transesterification reactions of cyanomethyl ester for synthesis of a 10-member macrolactone. In summary, the enantioselective annulation methodology of chiral allylsilane reagents offers a promising and novel approach to the synthesis of pyran containing natural products.

Acknowledgment. This paper is dedicated to Professor Dale Boger on the occasion of his 50th birthday. We are grateful to Prof. R. Jansen of the Gesellschaft für Bitechnologische Forschung for kindly providing an authentic sample of apicularen A and copies of ^{1}H NMR and ^{13}C NMR spectra. The authors are grateful to Prof. J. A. Porco Jr. for stimulating discussions. Financial support was obtained from the NIH GM55740. J.S.P. is grateful to Johnson & Johnson, Merck Co., Novartis, Pfizer, and GSK for financial support.

Supporting Information Available: Detailed experimental procedure, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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