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Formal Total Synthesis of (−)-Apicularen A via Transannular Conjugate Addition

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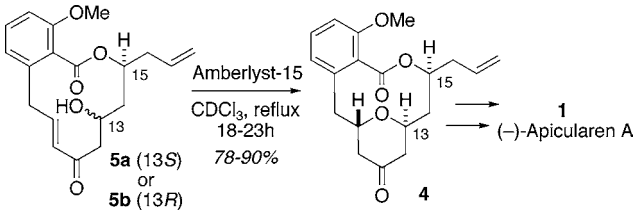
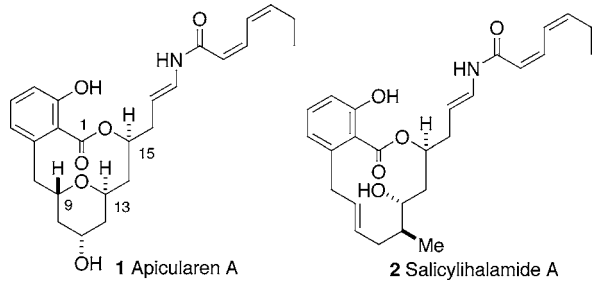
ABSTRACT



The formal total synthesis of the myxobacteria metabolite (−)-apicularen A (1) is described. The key step involved a novel acid-mediated transannular conjugate addition of the C13 hydroxyl into the α,β-unsaturated ketone in either of the macrolactones 5a or 5b to provide the same *trans*-pyranone 4. Conversion of 4 into the known apicularen intermediate diol 3 completed the formal synthesis.

The cytotoxin apicularen A (**1**) was isolated from extracts of the myxobacterium *Chondromyces robustus* by Höfle and co-workers.[1] Along with this compound, another less cytotoxic metabolite was found and identified as the *N*-acetyl-β-D-glucosamine glycoside of **1** named apicularen B. Interestingly, apicularen A (**1**) bears a striking resemblance to salicylihalamide A (**2**),[2] a novel metabolite isolated from a Western Australian marine sponge. Indeed, it is possible that the pyran ring in the apicularens may form by some type of transannular cyclization of a salicylihalamide-type precursor. Like the salicylihalamides, the apicularens contain a novel secondary enamide functionality which is probably critical for the biological activity[3] and also is found in other myxobacteria metabolites.[4] Apicularen A (**1**) shows highly effective growth inhibition of several human tumor cell lines originating from cervix (IC_{50} 0.4 $ngmL^{-1}$), kidney (IC_{50} 0.3 $ngmL^{-1}$), lung (IC_{50} 0.1 $ngmL^{-1}$), and prostate (IC_{50} 0.5 $ngmL^{-1}$) carcinomas.[1a]



The novel structure and biological activity of **1** have attracted the attention of several synthetic research groups, which has resulted in two total syntheses[5,6] and several formal syntheses.[7,8] A number of synthetic approaches to the apicularen ring system have also been reported.[9,10] A retrosynthetic analysis of compound **1** is depicted in Scheme 1. Apicularen A (**1**) has been previously synthesized by De

(1) (a) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913.

(2) (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. (b) Correction: Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **2001**, *66*, 1532.

(3) Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241.

(4) (a) Kunze, B.; Jansen, R.; Höfle, G.; Reichennach, H. *J. Antibiot.* **1994**, *47*, 881. (b) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085.

(5) (a) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069. (b) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217.

(6) (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701. (b) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. *Chem. Eur. J.* **2003**, *9*, 6177.

(7) (a) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549. (b) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104.

(8) Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357.

(9) Kühnert, S.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643.

(10) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, *43*, 8507.

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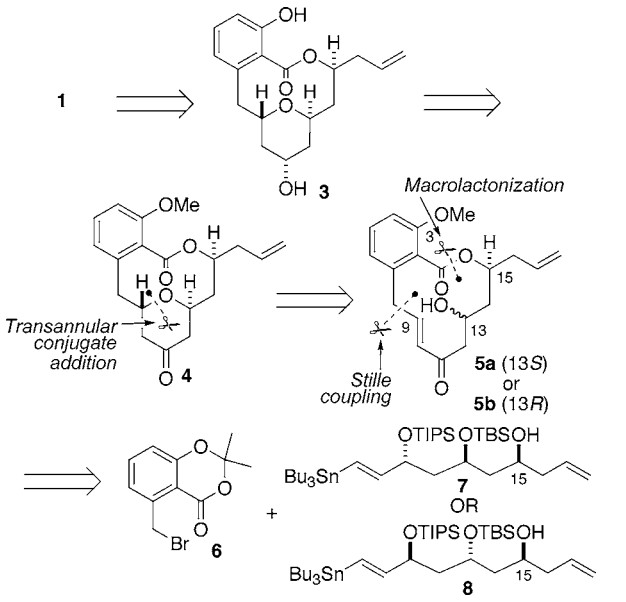
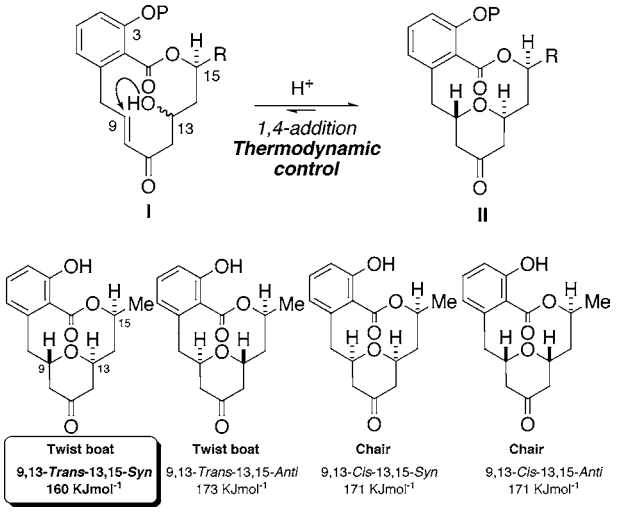
Scheme 1



Brabander and co-workers[5b] from the intermediate diol **3**, which in turn could be produced by reduction and demethylation of key intermediate ketone **4**. We envisaged that the pyran ring in **4** could be formed via a possible biomimetic transannular conjugate addition from the salicylihalamide-type precursor **5** as shown. Intermediate **5** could be obtained by Stille coupling[11] between the benzyl bromide **6** and either stannane **7** or **8** followed by a novel anion induced macrolactonization protocol.[5a] This method for the formation of the salicylihalamide-type ring system was utilized by us for a formal total synthesis of salicylihalamide A (**2**).[12]

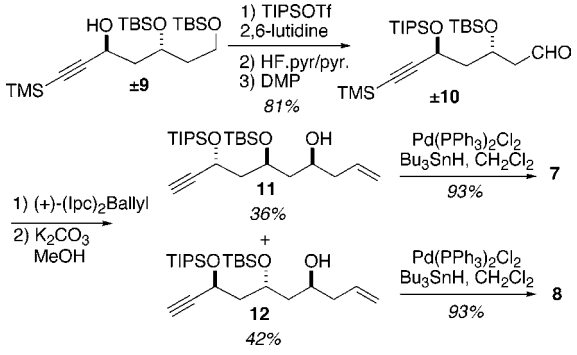
The pivotal pyranone formation reaction involves an intramolecular conjugate addition of the C13 oxygen into the C9−10 α,β-unsaturated ketone in precursor **I** that could produce the pyranone **II** with stereocontrol resulting from strain due to the preformed benzlactone (Scheme 2). MM2 calculations conducted on truncated apicularen-type ring systems[13] shown indicated that out of the four possible diastereoisomers that can be formed the 9,13-*trans*-13,15-*syn*-pyranone (twist-boat conformer)[14] is more stable than the others by more than 10 kJ mol^{-1}. Therefore, if a thermodynamic equilibrium could be established under acidic conditions,[10] formation of the 9,13-*trans*-13,15-*syn*-isomer **II** should be strongly favored. This means that the stereochemistry at C13 is not relevant and if opposite to that found in **1** [i.e., same as that found in salicylihalamide A (**2**)], it would epimerize since an equilibrium can involve an intermediate C13−C12 α,β-unsaturated ketone. In other words, a conjugate addition/elimination equilibrium would scramble the C9 and C13 stereocenters to result in stereoisomer **II** as the major product with all stereocontrol resulting from only the C15 center. Previous work on a model system has demonstrated this mode of cyclization forms the desired *trans*-pyranone almost exclusively.[10]

Scheme 2



Our approach to diol **3** began with the asymmetric synthesis of the cyclization precursor **5a** (Scheme 3). The

Scheme 3



known racemic propargylic alcohol ±**9**[10] was silylated, and deprotection of the primary TBS group followed by oxidation[15] provided aldehyde ±**10**. Racemic **10** was subjected to a Brown asymmetric allylation[16] reaction to install the C15 stereocenter, and subsequent alkyne deprotection provided the optically active diastereoisomers **11** and **12**, which were easily separated by flash chromatography. Each of these compounds was obtained in >95 ee as indicated by NMR analysis of their derived Mosher esters.[17] Palladium-catalyzed

(11) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (b) Farina, V.; Krishnamurthy V.; Scott W. J. In *Organic Reactions*; Paquette, L. A., Ed.; J. Wiley and Sons: New York, 1997; pp 1−652.

(12) Holloway, G.; Hügel, H.; Rizzacasa, M. A. *J. Org. Chem.* **2003**, *68*, 2200.

(13) PC MODEL.

(14) The X-ray structure of apicularen A revealed the tetrahydropyran was in a chair conformation; however, NMR studies indicated that the pyran is in a twist-boat conformation in solution. See ref 1b.

(15) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

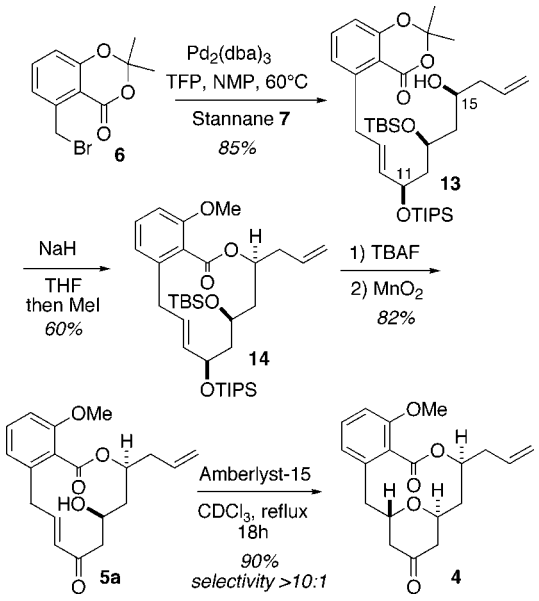
(16) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.

(17) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

hydrostannation[18] of alkynes **11** and **12** gave stannanes **7** and **8**, respectively. On the basis of the above hypothesis, either **7** or **8** can be used to synthesize pyranone **4**.

A Stille coupling[11] between the known bromide **6**[12] and stannane **7** produced the cyclization precursor **13** in good yield (Scheme 4). Treatment of a dilute solution of **13** with

Scheme 4



NaH[5a,12] resulted in smooth lactone formation with concomitant loss of acetone, and methylation of the resultant phenoxide in situ gave lactone **14**. It was found that the relative 11,13-*anti*-stereochemistry gave the best yields in the macrolactonization reaction. Interestingly, the C11 epimer of **13** failed to cyclize, and a TBS ether at C11 proved too labile. In addition, a free phenol at C3 interfered with the subsequent transformations so this was protected as a robust methyl ether. Global desilylation followed by selective allylic oxidation afforded enone **5a**. When **5a** was heated in $CDCl_3$ in the presence of Amberlyst-15,[10] smooth cyclization occurred to afford the desired *trans*-pyranone **4** as the major product (>10:1 selectivity) in excellent yield. ^{1}H NMR analysis of the progress of this reaction revealed two compounds are formed initially (9,13-*trans*-pyranone **4** and the corresponding *cis*-isomer) which eventually coalesce to one major compound **4** after 18 h. Compound **4** exhibited NOE interactions similar to those observed for apicularen A (**1**) itself (Figure 1). Furthermore, **4** was crystalline, and a single-crystal X-ray structure[19] confirmed the relative 9,13-*trans*-13,15-*syn*-stereochemistry (Figure 1). It is noteworthy that the X-ray structure of **4** shows the pyranone ring in a twist boat conformation which is opposite to that observed for **1**[1b] but compares to that observed for both **1** and **4** in solution.

(18) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(19) The X-ray structure of **4** was determined on the racemate. Crystallographic data have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. CCDC-233325.

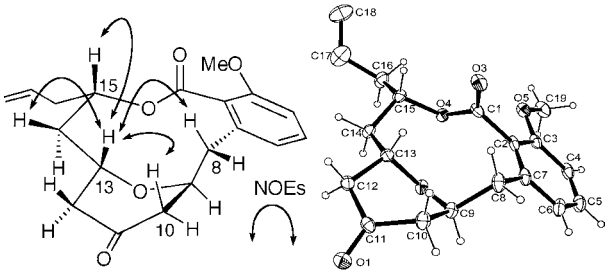
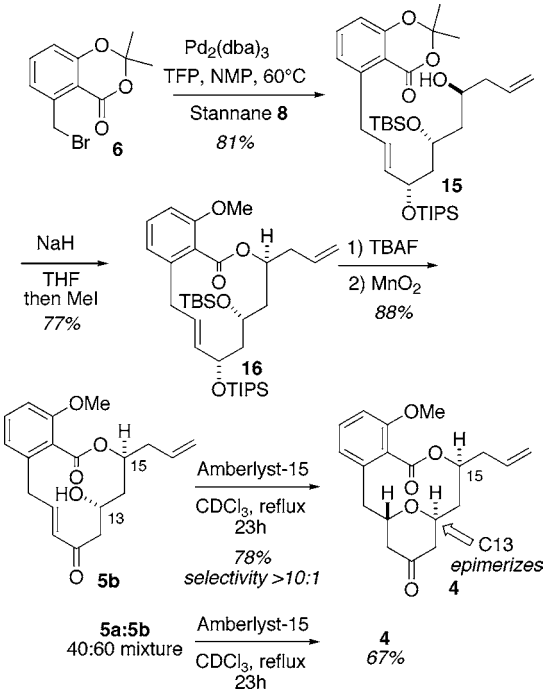


Figure 1. X-ray structure of **4**.

The enantiomer of pyranone (+)-**4** has been prepared previously by a different route as described by Taylor and co-workers.[7b] The data for our compound (+)-**4** matched that quoted in the literature except for the sign of the optical rotation [[α]$_D$ +138 (*c* 0.53, $CHCl_3$) (lit.[7b] [α]$_D$ −140 (*c* 0.60, $CHCl_3$))]. This result clearly shows the facile transannular cyclization results in the apicularen ring system in an efficient manner.

What remained was to demonstrate that the C13 epimer of **5a**, namely **5b** (13*R*), could be induced to cyclize to the *same* pyranone **4**. The route to the second cyclization precursor enone **5b** (13*R*) is shown in Scheme 5. Stille

Scheme 5



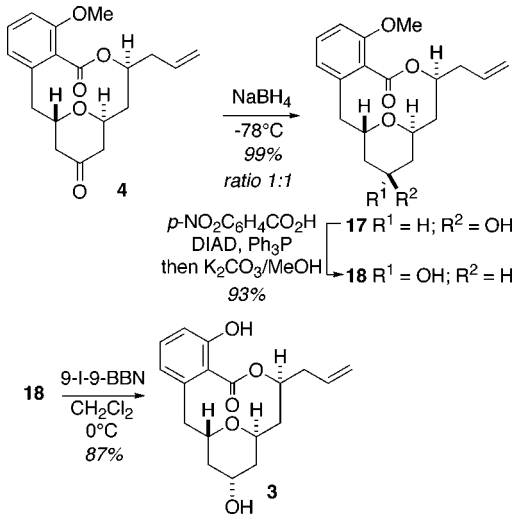
coupling[11] between bromide **6** and stannane **8** provided alkene **15** in high yield, and base-induced cyclization/methylation as described above afforded macrolactone **16**.

Desilylation and oxidation afforded the precursor **5b** ready for cyclization. To our delight, exposure of **5b** to acidic ion-

exchange resin in boiling $CDCl_3$ resulted in the formation of exactly the same pyranone **4** as that obtained by cyclization of **5a**. Thus, inversion at C13 had occurred to form the apicularen ring system in reasonable yield. This process was slightly less efficient than that described above for **5a**. Examination of the ^1H NMR spectrum during the cyclization equilibrium initially revealed a complex mixture. Again, these all eventually were converted into one major compound **4**. In a separate experiment, a mixture of **5a** and **5b** also cyclized under the same conditions to provide pyranone **4** as the major product (Scheme 5).

The final steps to diol **3** are detailed in Scheme 6. Stereoselective reduction of **4** proved difficult to achieve, so we resorted to reduction with $NaBH_4$, which proceeded in high yield albeit without any selectivity. The alcohols **17** and **18**[7b] were separated by silica gel chromatography, and the undesired isomer **17** was easily converted into the correct compound **18** via a modified Mitsunobu protocol.[20] Demethylation of **18** was effected by exposure to 9-I-9-BBN according to the procedure described by Taylor[7b] to afford diol **3** in high yield. The physical data for **3** was identical to the that reported in the literature[7,8,21] [$[\alpha]_D$ +5.6 (*c* 0.41, MeOH) (lit.[5a] $[\alpha]_D$ +6.8 (*c* 0.16, MeOH); lit.[8] $[\alpha]_D$ +5 (*c* 0.03, MeOH); lit. (enantiomer)[7b] $[\alpha]_D$ −4.5 (*c* 0.15, MeOH)]. This completes a formal total synthesis of (−)-apicularen A (**1**).

Scheme 6



In conclusion, we have achieved a formal total synthesis (−)-apicularen A (**1**)[22] which utilizes an efficient transannular conjugate addition to form the pyran ring whereby stereochemical outcome is under thermodynamic control. While these results do not confirm this mode of cyclization as biomimetic, the facile cyclization of **5a** and **5b** lends support to this proposal.[23]

Acknowledgment. We thank the Australian Research Council for funding.

Supporting Information Available: Characterization data for compounds **3**, **4**, **5a**,**b**, **7**, **8**, and **11**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0497943

(20) Mitsunobu, O. *Synthesis* **1981**, 1. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(21) An error in the ^{13}C NMR spectrum quoted for diol **3** in ref 5a was later corrected. See ref 7b.

(22) A third total synthesis of (−)-apicularen A (**1**) has recently been reported; see: Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425.

(23) For recent examples of biomimetic syntheses involving a thermodynamically controlled conjugate addition step, see: (a) Wood, J. L.; Jeong, S.; Salcedo, A.; Jenkins, J. *J. Org. Chem.* **1995**, *60*, 286. (b) Henschke, J. P.; Rickards, R. W. *Tetrahedron Lett.* **1996**, *37*, 3557.