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A New Stereocontrolled Synthetic Route to (−)-Echinosporin from D-Glucose via Padwa Allenylsulfone [3 + 2]-Anionic Cycloadditive Elimination

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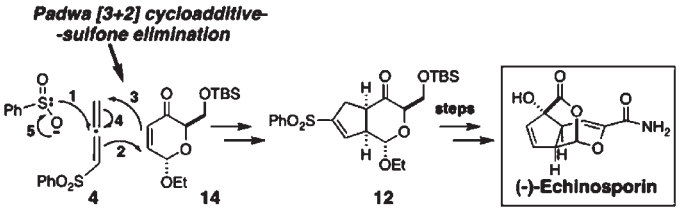
ABSTRACT



A new formal total synthesis of (−)-echinosporin has been developed based upon the Padwa [3 + 2]-cycloadditive elimination reaction of allenylsulfone 4 with the D-glucose-derived enone 14 which provides cycloadduct 12.

For some time now our group has been interested in the application of novel, under-exploited cycloaddition reactions in organic synthesis and, in this context, one process that recently came to our attention is the Padwa, sodium benzenesulfinate-induced, anionic [3 + 2]-cycloadditive elimination reaction of allenylsulfones with α,β-unsaturated carbonyl compounds,[1] a process that provides direct synthetic access to nonsymmetric cyclopentenylsulfones with complete regiocontrol. Despite the obvious synthetic advantages that can potentially accrue from use of this reaction, it has never been deployed successfully in any complex natural product total synthesis, notwithstanding the ease with which the resulting cyclopentenylsulfones can be synthetically manipulated.

Partly out of a desire to apply the Padwa [3 + 2]-cycloadditive elimination upon chiral dipolarophile systems, and partly out of our own natural curiosity to learn more about the scope and generality of this process, we set out to examine whether it could be performed stereoselectively on readily available, orthogonally protected monosaccharide-enones and ene-lactones. If it could, our aim was to use this chemistry in a new enantioselective total synthesis of the naturally occurring antitumor agent, (−)-echinosporin;[2] a challenging, highly strained, acetal-lactone of shikimate origin[2d] that has only succumbed to total synthesis once in Amos B. Smith's laboratory at Penn.[3,4]

Our initial efforts toward achieving this goal involved us investigating the Padwa [3 + 2]-cycloadditive elimination of ene-lactone **3** with (phenylsulfonyl)-1,2-propadiene (**4**)[5] to obtain the bicyclic adduct **6**, which would then be taken forward to (−)-echinosporin by a multistep synthetic sequence (Scheme 1). However, to our great dismay, the

(1) (a) Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 1617. (b) Padwa, A.; Yeske, P. E. *J. Org. Chem.* **1991**, *56*, 6386. (c) Padwa, A.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 3256. (d) Nunez, A., Jr.; Martin, M. R.; Fraile, A.; Garcia Romano, J. L. *Chem.—Eur. J.* **2010**, *16*, 5443.

(2) Isolation: (a) Sato, T.; Kawamoto, I.; Oka, T.; Okachi, R. *J. Antibiot.* **1982**, *35*, 266. (b) Hirayama, N.; Iida, T.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 287. Bioactivity: (c) Morimoto, M.; Imai, R. *J. Antibiot.* **1985**, *38*, 490. Biosynthetic studies on (−)-echinosporin: (d) Dubeler, A.; Krastel, P.; Floss, H. G.; Zeeck, A. *Eur. J. Org. Chem.* **2002**, 983.

(3) Total synthesis of (−)-echinosporin: (a) Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039. (b) Smith, A. B., III; Sulikowski, G. A.; Sulikowski, M. M.; Fujimoto, K. *J. Am. Chem. Soc.* **1992**, *114*, 2567.

(4) For various other synthetic approaches to echinosporin, see: (a) Kinsella, M. A.; Kalish, V. J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 105. (b) Forst, J. M. M.S. Thesis, University of Minnesota, 1987. (c) Wincott, F. E. Ph.D Thesis, Yale University, 1989.

(5) Stirling, C. J. M. *J. Chem. Soc.* **1964**, 5856.

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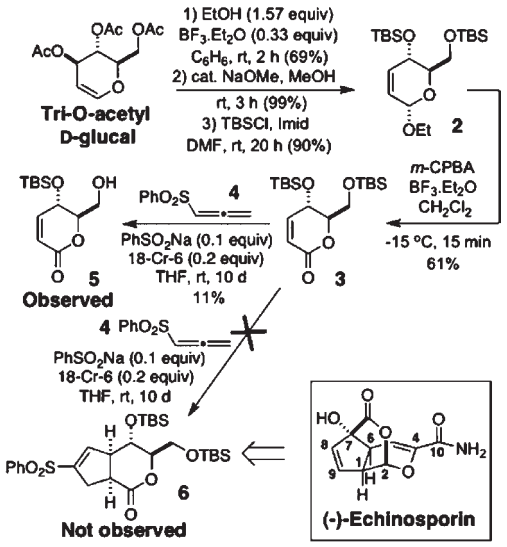
Scheme 1. Our Initial Failed Attempt at Applying the Padwa Allenylsulfone [3 + 2]-Cycloadditive Elimination in the Synthesis of (−)-Echinosporin



attempted cycloadditive elimination between **3** and **4** did not produce **6**. Instead, the O-desilylated ene-lactone **5** was the only significant product formed in a meager 11% yield.

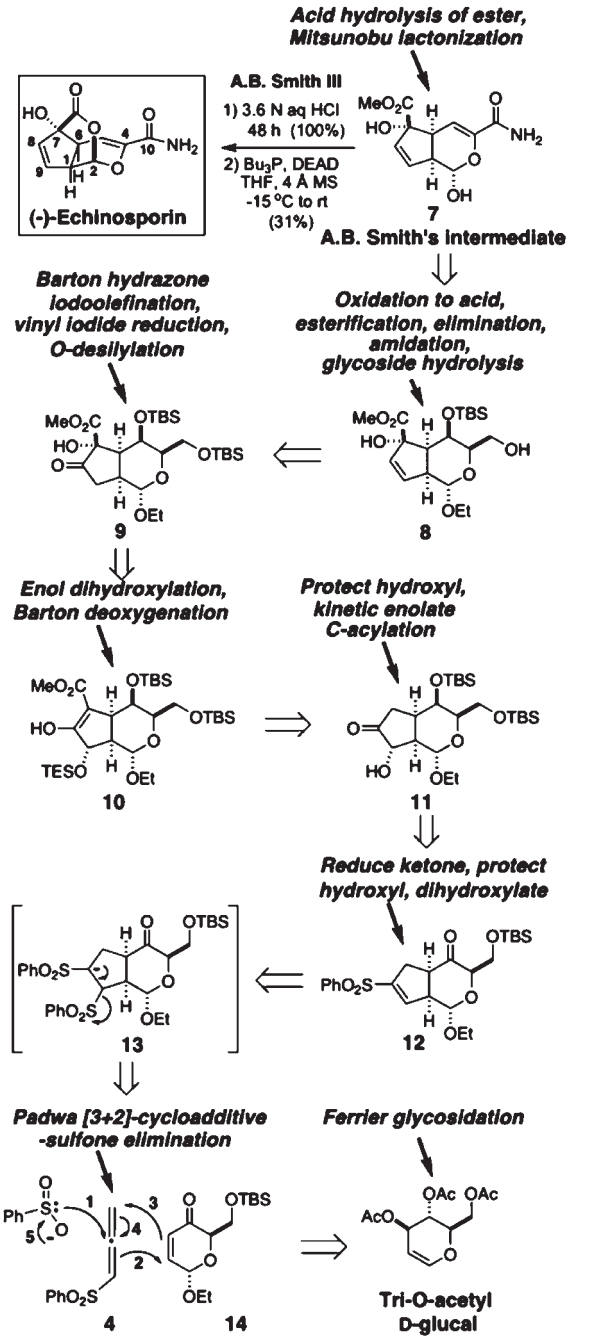
In light of this outcome, we modified our synthetic approach to that shown in Scheme 2. In this, (−)-echinosporin would derive from Smith's advanced synthetic intermediate **7**[3] which itself would be prepared from the primary alcohol **8** and its progenitor **9**, whose C(7)-tertiary-hydroxyl we envisioned installing through the dihydroxylation of **10** on its less hindered underside. The centerpiece of our plan would be the alternate, regiochemically reversed Padwa [3 + 2]-cycloadditive elimination[1] between the more electrophilic pyranoside enone **14**[6] and allenylsulfone **4**[5] which we believed would yield **12** which itself would potentially be convertible into **10** via **11**.

Enone **14** was secured (Scheme 3) by a modification of a route originally developed by Card[6] which initially entailed us performing a Ferrier glycosidation on tri-*O*-acetyl-D-glucal with ethanol and $BF_3 \cdot Et_2O$, O-deacetylating the product with NaOMe/MeOH, and then selectively *O*-silylating the 4,6-diol with TBSCl and imidazole in DMF. A Swern oxidation on **15** thereafter secured **14** in 60% overall yield in four steps.

The key anionic Padwa [3 + 2]-cycloadditive elimination was best conducted with a 4.5-fold excess of the enone **14**, relative to the allenylsulfone **4**,[5] and it was accomplished in 56% yield on a 60 g scale. The process was fully stereocontrolled. It also typically allowed 81% of the theoretically isolable starting enone **14** to be recovered after SiO_2 flash chromatography of the crude reaction mixture. A

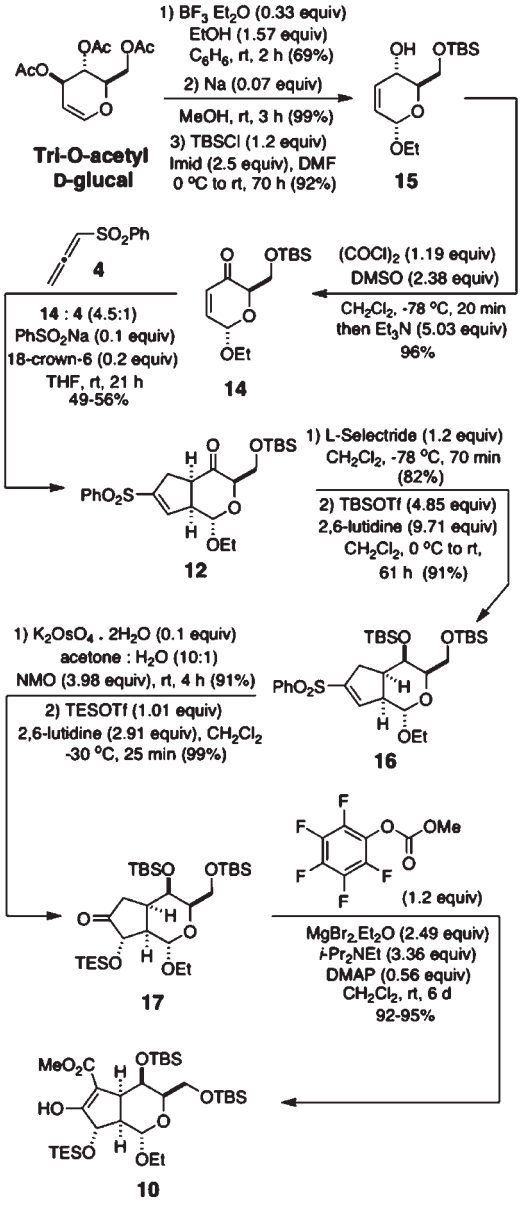
(6) (a) For its previous use in stereoselective [4 + 2]-cycloaddition, see: Card, P. J. *J. Org. Chem.* **1982**, *47*, 2169. (b) For Trost's seminal use of **14** in a stereoselective [3 + 2]-cycloaddition, see: Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.

Scheme 2. Revised Retrosynthetic Plan for the Formal Total Synthesis of (−)-Echinosporin



chemo- and stereoselective reduction of the ketone in **12** ensued with Li-tri*sec*-butylborohydride (L-Selectride) in CH_2Cl_2. Here, the upward-pointing cyclopentenylsulfone and the $-CH_2OTBS$ group both guaranteed an exclusive underside delivery of the hydride ion to the keto group to provide **16** following *O*-silylation. Potassium osmate thereafter induced underside *syn*-dihydroxylation to give the α-hydroxy ketone as the sole product, and this was *O*-triethylsilylated with TESOTf and 2,6-lutidine at −30 °C for 25 min. We next examined a variety of methods for the kinetic enolization of ketone **17** at C(7) including

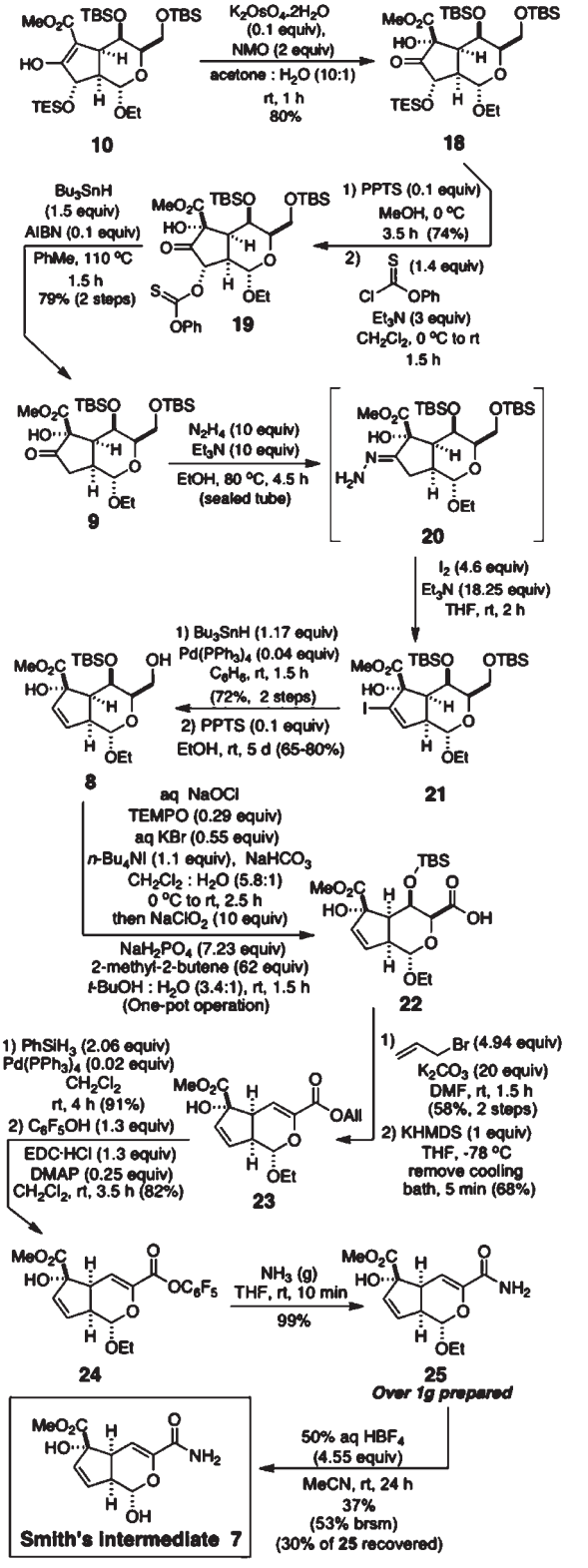
Scheme 3. Synthesis of the β-Keto Ester **10**



with LiHMDS and Mander's reagent[7] in THF at −78 °C, and LDA/methoxycarbonyl imidazolide[8] in THF at −78 °C and then at rt, but we did not obtain a satisfactory outcome. Eventually, after much experimentation, we discovered that methyl pentafluorophenyl carbonate in the presence of $MgBr_2 \cdot Et_2O$, Hunig's base, and DMAP[9] in CH_2Cl_2 could effect the desired *C*-acylation efficiently. Significantly, this new method for β-keto ester synthesis produced **10** in 92−95% yield.

The time had now come for C(7)-tertiary alcohol installation, which was best accomplished through the dihydroxylation of **10** with potassium osmate and NMO (Scheme 4); it furnished **18** as a single product in 80% yield.

Scheme 4. Completion of Our Formal Synthesis of (−)-Echinosporin



(7) Mander, L.; Sethu, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(8) Li, Y.; Hale, K. J. *Org. Lett.* **2007**, *9*, 1267.
(9) (a) Brooks, D. W.; Lu, L. D.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72. (b) Lim, D.; Zhou, G.; Livanos, A. E.; Fang, F.; Coltart, D. M. *Synthesis* **2008**, 2148.

(10) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

The TES-group was next detached from **18** with PPTS/MeOH, and a Barton–McCombie[10] deoxygenation was performed. Ketone **9** was now subjected to Barton's excellent iodoolefination procedure,[11] which entailed us converting the ketone into a hydrazone and treating this with iodine and triethylamine. Stille Pd(0)-induced reductive cross-coupling with Bu_3SnH[12] thereafter deiodinated **21** to give the desired cyclopentene in 72% overall yield. Its primary TBS group was detached with PPTS/EtOH over 5 days to obtain **8** in 65–80% yield. Alcohol **8** was immediately oxidized to the acid **22** in a one-pot operation[13] prior to *O*-allylation. A carefully timed (*only* 5 min) E1cb elimination of this ester followed, using KHMDS (*only* 1 equiv) at low temperature.

O-Deallylation of **23** with phenylsilane and Pd(0)[13] subsequently unmasked the acid, to allow formation of the pentafluorophenyl ester **24** with EDC·HCl (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride) and pentafluorophenol. The final steps of our new (−)-echinosporin formal total synthesis involved ammonolysis and intersection with Smith's penultimate intermediate **7**.[3] The latter chemoselective deprotection was best accomplished by reacting **25** with 50% aqueous HBF_4,[15] a reaction which, for ease of final product purification, was best stopped at ∼50% conversion. By utilizing this method, hemiacetal **7** could be reproducibly obtained pure in 37% yield, or 53% yield based upon a 30% recovery of the starting glycoside **25**. Importantly, our version of **7** matched Smith's previously reported NMR data perfectly (see Supporting Information), as did its di-*O*-acetate derivative in $CDCl_3$.[3]

In conclusion, with the new enantioselective route that we have developed to (−)-echinosporin, we have demonstrated the great worth of the Padwa allenylsulfone [3 + 2]-cycloadditive elimination reaction in complex natural product total synthesis for the first time. We have also uncovered a useful new protocol for the α-*C*-acylation of bromomagnesium ketone enolates. Further details of the wide scope of this new enolate *C*-acylation method will be reported in due course, including with other alkyl pentafluorophenyl carbonates, thiocarbonates, and thionocarbonates.

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Supporting Information Available. Detailed experimental procedures and spectral data, as well as copies of the 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra (1D and 2D), IR, and HR mass spectra of all compounds in the synthetic route, are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

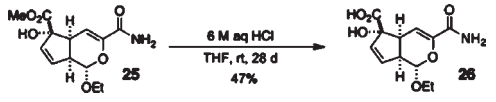
(11) (a) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470. (b) Barton, D. H. R.; Chen, M.; Jaszberenyi, J. C.; Taylor, D. C.; Hartz, R. A.; Smith, A. B., III. *Org. Synth.* **1998**, *74*, 101.

(12) (a) Taniguchi, M.; Takeyama, Y.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2593. (b) Uenishi, J.i.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965.

(13) For the one-pot Piancatelli/Pinnick oxidation, see: Huang, L.; Teumelson, N.; Huang, X. *Chem.—Eur. J.* **2006**, *12*, 5246.

(14) Dessolin, M.; Guillerez, M.-G.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741.

(15) When we attempted to convert the ethyl glycoside **25** into the hemiacetal **7** using 6 M aqueous HCl in THF at rt for 28 days, the reaction was unsuccessful. Instead, the corresponding α-hydroxy carboxylic acid **26** was isolated in 47% yield (see the SI for its NMR spectra):



The authors declare no competing financial interest.