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Diastereoselective Phenol *para*-Alkylation: Access to a Cross-Conjugated Cyclohexadienone en Route to Resiniferatoxin

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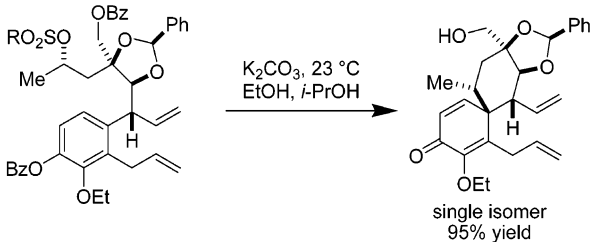
ABSTRACT



We document a route for the synthesis of a densely functionalized spiro-fused 2,5-cyclohexadienone as an intermediate for the synthesis of resineferatoxin. The strategy is based on an unprecedented diastereoselective, intramolecular phenol *para*-alkylation to a cross-conjugated cyclohexadienone. In the course of these synthetic studies we developed rapid access to a chiral nitrile possessing a quaternary stereocenter and disclose an unusual acetal rearrangement from a dioxane, which favors the corresponding dioxepane.

The diterpene natural product resiniferatoxin (**1**, Figure 1) is a prominent member of the daphnane structure class, in large part because of its high irritant activity.[1] The structurally related tigliane phorbol has inspired great innovation in the field of organic synthesis over the past 30 years, resulting in completed total syntheses of both resiniferatoxin and phorbol.[2] We have demonstrated that the daphnane structure class could be accessed quickly through the photorearrangement of tricyclic cross-conjugated 2,5-cyclohexadienones (eq 1).[3,4] In this letter we report our results in the development and synthesis of densely functionalized bicyclic cyclohexadienone-ring systems in our efforts to gain fast access to a variety of different photoprecursors for their use in the synthesis of daphnanes and tiglianes. In the course of the synthetic studies we have made a number of interesting observations: (1) a highly diastereoselective *para*-alkylation

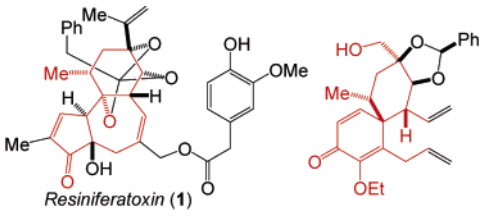
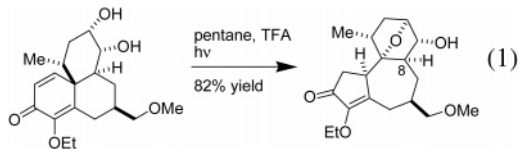


Figure 1. The daphnane resiniferatoxin with a cyclohexadienone.



(1)

(1) (a) Appendino, G.; Szallasi, A. *Life Sci.* **1997**, *60*, 681. (b) Szallasi, A.; Blumberg, P. M. *Pain* **1996**, *68*, 195.

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of a phenol, (2) the use of a chiral nitrile-substituted dioxane to establish a quaternary center, and (3) an unusual rearrangement of a hydroxylmethyl-substituted dioxane that favors the formation of the seven-memberred ring acetal.

As part of a projected investigation of the photochemistry of cross-conjugated cyclohexadienones in the context of the synthesis of resineferatoxin and analogues, we designed a strategy to access a highly functionalized carbocyclic core distinct from the route we had previously employed for the tricyclic system. We aimed at a route in which an intramolecular, diastereoselective phenol *para*-alkylation[5] would generate the requisite bicyle incorporating the cyclohexadienone chromophore. In this approach the stereogenic center C-11 (Figure 2, resiniferatoxin numbering) would be set by

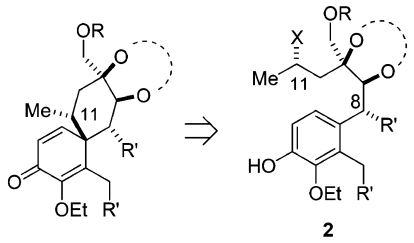
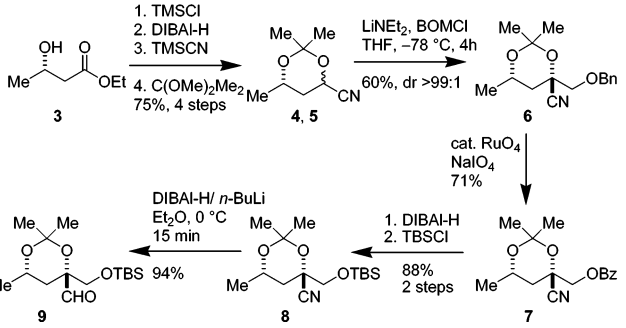


Figure 2. Retrosynthetic analysis for the formation of the cyclohexadienone via diastereoselective Winstein alkylation.

appropriate selection of the starting material **2** and trans formed to the product through an invertive displacement. By contrast, the configuration at the quaternary center necessarily needs to be controlled in the alkylation reaction. Our previous study provided little guidance in this respect, because the bicyclic intermediate dictated the facial selectivity in the intramolecular alkylation. A stereoselective phenol *para*-alkylation in an unconstrained acyclic intermediate has not been previously addressed, and thus we became interested in investigating the stereochemical consequences of this critical step.

In selecting a viable route to the C-8−C-11 fragment (**2**, Figure 2), we decided to employ the method developed by Rychnovsky for the synthesis of protected 1,3-diol units.[6] Unlike the reported uses of this elegant chemistry in which the nitrile is excised to give a methine stereocenter, however, we aimed to retain the quaternary stereocenter and transform the nitrile into an aldehyde. The synthesis of **9** commenced with commercially available (*S*)-3-hydroxy butyric acid ethyl ester (**3**) (Scheme 1). The hydroxyl butyrate was protected

Scheme 1



as its trimethylsilyl ether, and the resulting ester was reduced to the aldehyde (DIBALH). Subsequent cyanide-catalyzed trimethylsilyl cyanide addition to the aldehyde followed by ketal formation afforded the two diastereomeric acetonides **4** and **5** in 75% combined yield over four steps. Alkylation of the derived nitrile enolate with benzyl chloromethyl ether (BOMCl) afforded the desired ether **6** in 60% yield as a single diastereomer as assayed by analysis of the ^{1}H NMR spectrum. The reaction sequence (**3** → **6**) could conveniently be accomplished on a 100-g scale. Further functionalization of the benzyl-protected primary alcohol ultimately required cleavage of the benzyl ether. We found this deprotection step to be problematic under reductive conditions (Na/NH_3, H_2/Pd) at this as well as at later stages in the synthesis. However, selective C−H oxidation using RuO_4/$NaIO_4$[7] transformed the benzyl ether to the corresponding benzoate **7**. Reduction of this benzoate with DIBALH and protection of the resulting alcohol as its *tert*-butyldimethylsilyl ether afforded nitrile **8** in 88% yield. Nitrile reduction to aldehyde **9** using DIBALH, a common reducing agent for this transformation,[8] afforded the product in only 30−40% yield. However, using the aluminate complex formed from *n*-BuLi and DIBALH,[9] the desired aldehyde could be isolated in 94% yield.

The synthesis of the requisite coupling partner for **9**, cinnamyl bromide **10**, was pursued next (Scheme 2). The synthesis started with regioselective acetylation of inexpensive 3,4-dihydroxybenzaldehyde (**11**) to afford the mono 3-acyl ester along with its 4-acyl regioisomer as a 9:1 mixture in 66% yield after recrystallization. Protection of the residual phenol group as its methanesulfonic acid ester yielded benzaldehyde **12**. Horner−Wadsworth−Emmons reaction with

(2) Phorbol: (a) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957. (c) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897. (d) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590. Resiniferatoxin: Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976.

(3) Jackson, S. R.; Johnson, M. G.; Mikami, M.; Shiokawa, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2694.

(4) For the closely related photorearrangement of α-santonin, see: (a) Barton, D. H. R.; DeMayo, P.; Shafiq, M. *J. Chem. Soc.* **1957**, 929; *J. Chem. Soc.* **1958**, 141; *J. Chem. Soc.* **1958**, 3314; *Proc. Chem. Soc.* **1957**, 205. (b) Arigoni, D.; Bosshard, H.; Bruderer, H.; Büchi, G.; Jeger, O.; Krebaum, L. J. *Helv. Chim. Acta* **1957**, *40*, 1732.

(5) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756.

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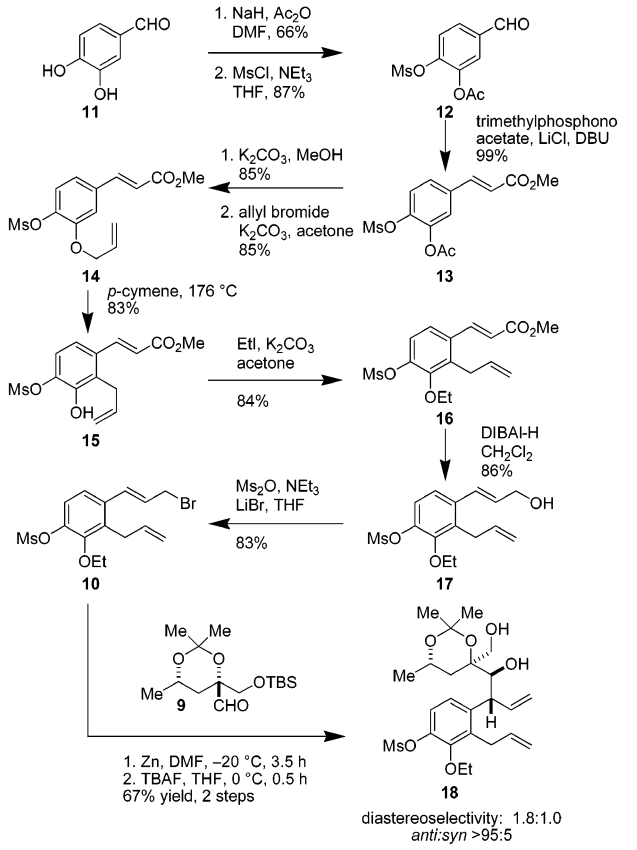
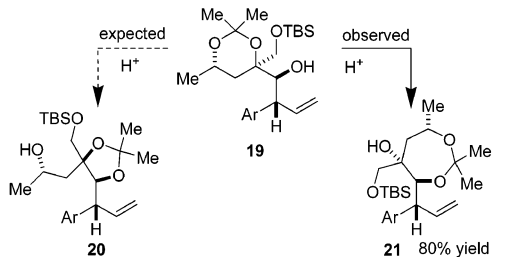
Scheme 2



trimethyl-phosphono acetate[10] furnished ethyl cinnamate **13** in 99% yield. Methanolysis of the acetate followed by *O*-allylation gave **14** in 72% yield over two steps. Claisen rearrangement proceeded smoothly in refluxing *p*-cymene. Ethylation of the phenol functionality gave ethyl cinnamate **16,** which was reduced to cinnamyl alcohol **17** (60% yield over three steps). Treatment of this alcohol with mesyl anhydride and LiBr furnished cinnamyl bromide **10**. The use of the mesylate as a phenol protecting group in **10** is essential for the stability of the cinnamyl bromide.[11]

Treatment of **10** with activated zinc in DMF at −20 °C furnished an intermediate allyl zinc, which underwent addition to aldehyde **9** to afford **19**. It was most convenient to determine the yield of the addition reaction following desilylation; thus **18** was isolated in 41% yield, after two steps.

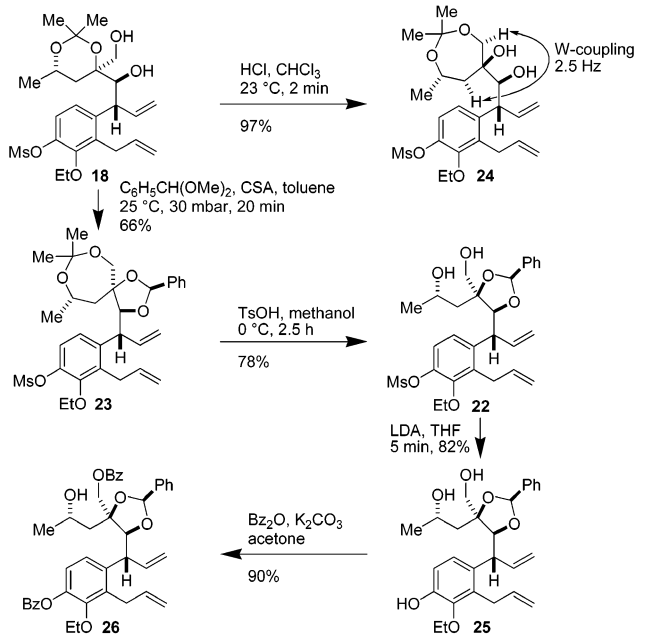
Initially, we envisaged rearranging the six-membered isopropylidene ketal **19** to the five-membered isopropylidene ketal **20** (eq 2). Such rearrangements are generally favorable,



(2)

because 1,3-*syn*-diaxial interactions in the [1,3]-dioxane ring are avoided in the corresponding five-membered heterocycle.[12] To our surprise, acid-catalyzed rearrangement of **19** did not afford the expected [1,3]-dioxolane **20** but instead [1,3]-dioxepane **21** in 80% yield. In seven-membered carbocycles, an important source of strain results from transannular interactions wherein substituents on opposite sides of the ring may approach within van der Waals distances. This unfavorable interaction is in large part responsible for the strain energy of cycloheptane of 6.2 kcal/mol.[13] In [1,3]-dioxepanes this transannular interaction is in part attenuated, because one hydrogen atom in the carbocycle is replaced by a lone pair in the heterocycle. The observation of the unusual ketal rearrangement was fortuitously exploited in the synthesis of diol **22** (Scheme 3). Isopropylidene ketal

Scheme 3



18 underwent acid-catalyzed rearrangement to the corresponding dioxepane, and the resulting diol protected with benzaldehyde dimethyl acetal to give dioxepane **23**. To confirm the structure of the initially formed rearrangement product, [1,3]-dioxepane **24** was prepared by HCl-catalyzed ketal transposition of diol **18**.

Analysis of the ^{1}H NMR and COSY NMR spectra of **24** gave instructive information about the conformation of the

(10) (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber*. **1959**, *92*, 2499. (b) Wadsworth, W.; Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733. (c) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett*. **1984**, *25*, 2183.

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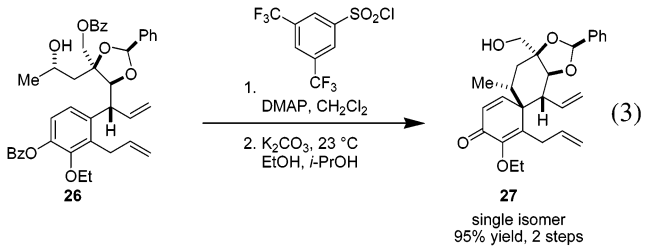
(13) Anet, F. A. L. Medium-Sized Oxygen Heterocycles. In *Conformational Analysis of Medium Sized Heterocycles*; Glass, R. S., Ed.; VCH Publishers: New York, 1988.

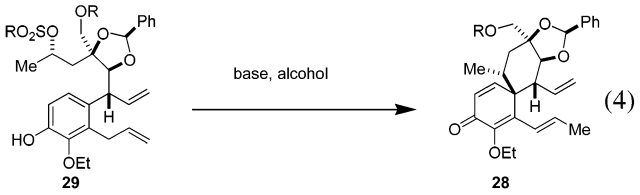
dioxepane. Strong W-coupling of 2.5 Hz between the two equatorial hydrogen atoms of both methylene groups in the seven-membered ring indicated a rigid chair conformation. Subsequent acid-catalyzed methanolysis of the more labile isopropylidene ketal in the presence of the benzylidene acetal in **23** furnished diol **22**. LDA-mediated cleavage of the aryl methanesulfonate[11] to phenol diol **25** followed by selective bisbenzoylation afforded **26**.

For the crucial phenol *para*-alkylation, the secondary alcohol in **26** needed to be converted into a good leaving group. After sulfonylation of the alcohol as its 3,5-bistrifluoromethylbenzenesulfonate ester, the key transformation could be promoted by K_2CO_3 in 2-propanol/ethanol at 23 °C, and the desired spirocycle **27** could be isolated in 95% yield over two steps (eq 3). Most importantly, the reaction



(3)

afforded the product including a new quaternary stereogenic center diastereoselectively. Hence, the product cyclohexadienone was isolated as a single isomer as assayed by ^{1}H NMR. The observed selectivity at the quaternary stereocenter can be rationalized by analysis of the two diastereomeric transition states depicted in Figure 3. An unfavorable *syn*-pentane-like interaction renders **B** significantly higher in energy with respect to **A** and thus accounts for the high selectivity. Of additional importance, careful choice of solvent mixture and base proved essential to obtain the optimized reaction outcome. The use of methanol as solvent accelerated the reaction but delivered substantial amounts of material resulting from double-bond isomerization to produce conjugated enone **28** (eq 4) (ratio **27** to **28**: 2/3).



(4)

The same observations could be found with ethanol as solvent, albeit to a smaller extent (ratio 4/1). 2-Propanol dramatically reduced the overall rate of reaction and thus was not practical. K_2CO_3 was found to be the optimal base, because weaker bases such as triethylamine did not initiate the reaction and stronger bases such as NaOMe, KO*t*-Bu, and Cs_2CO_3 resulted in double-bond isomerization.

In conclusion, we have documented a route that provides rapid access to densely functionalized spiro-fused cyclohexadienones through a novel series of transformations. Key to the successful approach was a highly diastereoselective phenol *para*-alkylation, which affords the desired spirocycle as a single diasteomer in 95% yield, generating an otherwise difficult-to-prepare quaternary center. The combination of the phenol alkylation with the unexpected formation of a dioxepane-derived acetal and the nitrile alkylation chemistry yields a serviceable strategy. We are in a position to prepare a variety of cyclohexadienones and examine their behavior in photorearrangement reactions to provide useful intermediates for the synthesis of daphnane and tigliane structures.

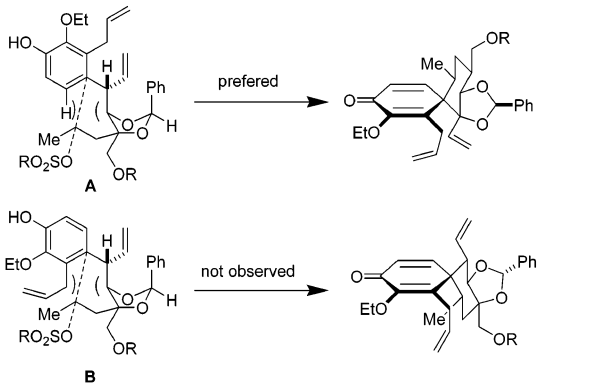


Figure 3. Rationale for the selectivity in the phenol *para*-alkylation illustrated by the diastereomeric transition states **A** and **B**.

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Supporting Information Available: Experimental details and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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