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Highly Regioselective Diels–Alder Reactions toward Oroidin Alkaloids: Use of a Tosylvinyl Moiety as a Nitrogen Masking Group with Adjustable Electronics

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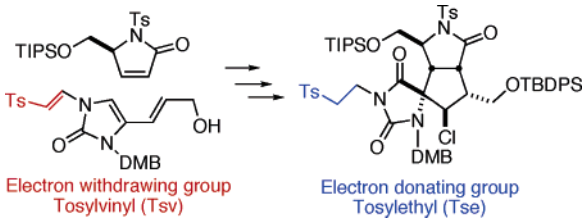
ABSTRACT



The use of the *p*-toluenesulfonyl (Ts) and tosylvinyl (Tsv) groups as nitrogen masking groups imparted high regioselectivity in Diels–Alder reactions directed toward members of the oroidin-derived marine alkaloid family. The electron-withdrawing Tsv group was utilized as an electronically adjustable nitrogen-protecting group as subsequent hydrogenation provided the more electron-rich tosylethyl (Tse) group. This electronic adjustment strategy avoided a protecting group exchange and provided the required electronics for the key chlorination/ring-contraction sequence.

The development of protecting groups for organic synthesis that more precisely control chemoselectivity continues to drive new advances. However, recent reports demonstrate the potential of additional utility for protecting groups. For example, the recent development of the *p*-nitrobenzenesulfonyl group (nosyl) by Fukuyama illustrates a new direction toward the development of protecting groups with dual roles including facilitating removal and altering reactivity, e.g., for nitrogen alkylation via Mitsunobu processes.[1] Protecting groups that alter the reactivity and sometimes regioselectivity of substrates have proven useful for a variety of reactions including Diels−Alder reactions and electrophilic aromatic substitution (e.g., acyl groups on phenols or anilines). In our ongoing studies[2] toward the synthesis of oroidin-derived alkaloids,[3] we faced a situation that required the development of a nitrogen-protecting group with readily adjustable electronic properties. Herein, we describe an application of the electron-poor *p*-tosylvinyl (Tsv) group that is readily converted to the more electron-rich *p*-tosylethyl (Tse) group.[4] This strategy was applied to our Diels−Alder/chlorination/ring contraction approach to the oroidin alkaloids,[2a] in particular the palau'amines (**2**−**4**)[5] and the axinellamines (**8**−**11**) (Figure 1).[6]

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(1) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

(2) (a) Dilley, A. S.; Romo, D. *Org Lett.* **2001**, *3*, 1535. (b) Poullennec, K.; Romo, D. *Org. Lett.* **2002**, *4*, 2645. (c) Poullennec, K.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344.

(3) For a recent review of oroidin-derived alkaloids, see: Hoffmann, H.; Lindel, T. *Synthesis* **2003**, *12*, 1753.

(4) For a lead reference to the use of the Tse group for nitrogen protection including conditions for its removal, see: Dastrup, D. M.; Yap, A. H.; Weinreb, S. M.; Henry, J. R.; Lechleiter, A. J. *Tetrahedron* **2004**, *60*, 90.

(5) (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281.

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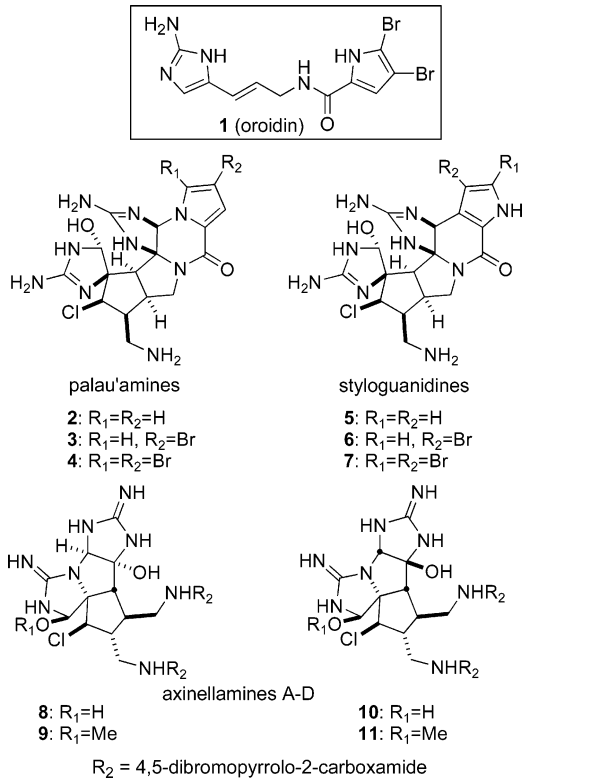
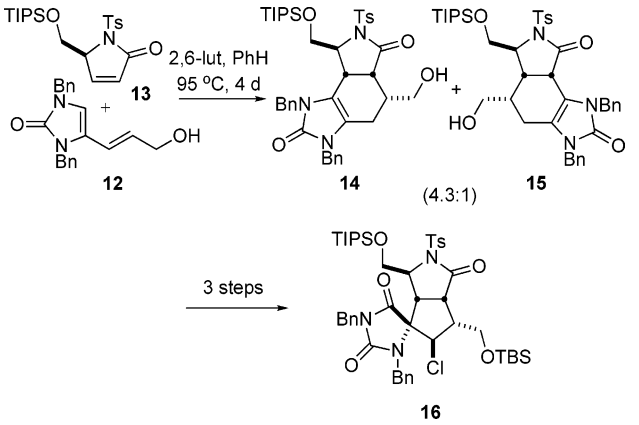


Figure 1. Structure of oroidin and oroidin-derived sponge alkaloids.

Several groups have described synthetic approaches to the axinellamines and palau'amines including those of Overman,[7] Carreira,[8] Lovely,[9] and Austin.[10] Our synthetic approach to this class of bisguanidine alkaloids is based on the biosynthetic hypothesis proposed by Kinnel and Scheuer.[5a,11] Al-Mourabit and Potier[13] and most recently Baran have posited alternative biosynthetic proposals.[12] These metabolites are thought to be biosynthesized from a common precursor, oroidin **1**.[3,13] In our synthetic strategy, a key Diels−Alder/oxidation/tandem chlorination−1,2-shift sequence resulted in a four-step enantioselective assembly of the densely functionalized spirocyclic core **16** from benzyl-protected vinyl imidazolone **12** and lactam **13** (Scheme 1).[2a] While

Scheme 1. "Biomimetic" Synthesis of the Diastereomeric Spirocyclic Core Found in the Axinellamines and Palau'amine[2a]



the Diels−Alder process gave predominantly the desired regioisomer **14** (4.3:1 ratio, **14**/**15**) with concomitant double-bond isomerization, we sought to improve the regioselectivity by altering the electronics of the nitrogen-protecting groups on the diene. Attempts to improve regioselectivity by use of Lewis acids were unsuccessful due to the instability of diene **12** to acid. Optimal yields were obtained without Lewis acid and with 2,6-lutidine added to scavenge adventitious acid.

We reasoned that use of an electron-withdrawing group on N^1 while maintaining an electron-donating group on N^2 would perturb the orbital coefficients of the diene leading to improved regioselectivity (Figure 2). This analysis prompted

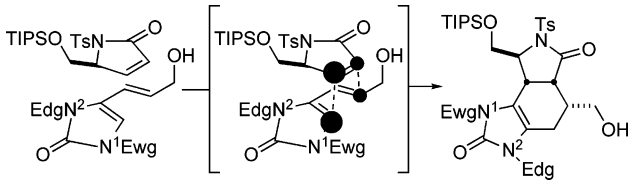


Figure 2. Electronics of vinyl imidazolones as dienes.

us to study the *p*-toluenesulfonyl (Ts) group as an electron-withdrawing group for N^1 and a 3,4-dimethoxybenzyl (DMB) group[14] as an electron-rich group on N^2 leading to diene **17** (Scheme 2). This diene was prepared in an analogous manner to the dibenzylated diene described previously.[2a,15] Subsequent Diels−Alder reaction of this diene with lactam **13** under thermal conditions resulted in the formation of two compounds. Further prolonged heating at slightly elevated temperatures (114 °C) *indeed led to the isolation of a single regioisomer **19** in 75% yield* (Scheme 2). Thus, the tosyl group at N^1 had perturbed the orbital coefficients of the diene

(6) (a) Urban, S.; Leone, P. D. A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem*. **1999**, *64*, 731. (b) The same name was previously given to a simpler pyrrole alkaloid; see: Bascombe, K. C.; Peter, S. R.; Tinto, W. F.; Bissada, S. M.; McLean, S.; Reynolds, W. F. *Heterocycles* **1998**, *48*, 1461.

(7) (a) Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Am. Chem. Soc*. **1997**, *119*, 7159. (b) Belanger G.; Hong F.-T.; Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Org. Chem*. **2002**, *67*, 7780. (c) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559.

(8) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc*. **2000**, *122*, 8793.

(9) (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett*. **2001**, *3*, 1319. (b) Lovely, C. J.; Du, H.; Dias, H. V. R *Heterocycles* **2003**, *60*, 1. (c) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett*. **2003**, *5*, 3623.

(10) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Lowe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett*. **2003**, *5*, 2203.

(11) This biosynthetic proposal was suggested by a reviewer of the manuscript by Kinnel and Scheuer (ref 5a).

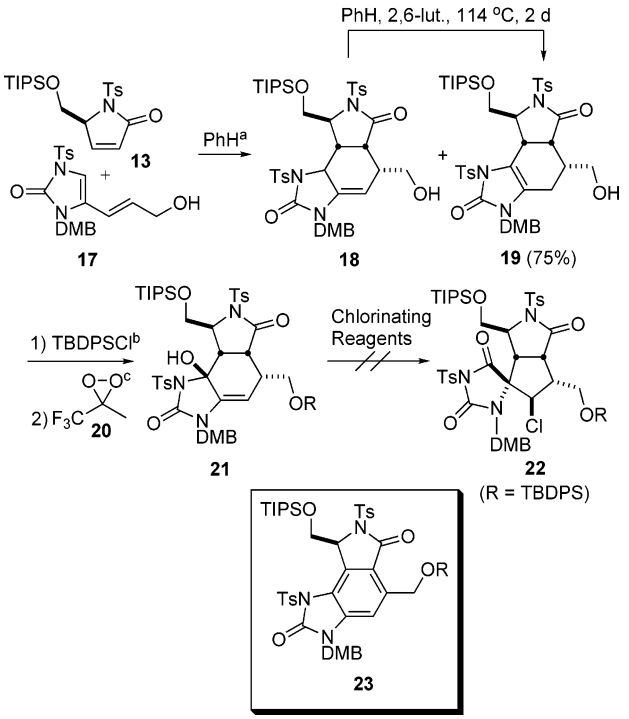
(12) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed*. **2004**, *43*, 2674.

(13) (a) Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem*. **2001**, 237.

(14) Difficulties in removing the benzyl group under mild conditions in similar substrates led to the use of the 3,4-dimethoxybenzyl group.

(15) See the Supporting Information for details.

Scheme 2. Improved Regioselectivity in the Diels−Alder Reaction with Diene **17** and Subsequent Transformations[a]

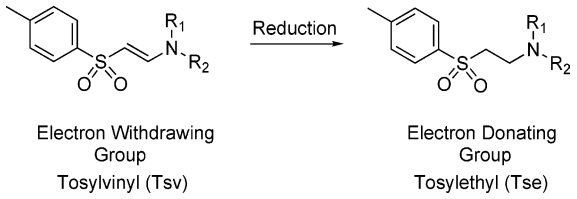


[a] Reagents and conditions: (a) 2,6-lutidine, 95 °C, 2 d (75%); (b) DMAP, Et_3N, CH_2Cl_2, (93%); (c) CH_2Cl_2, $MgSO_4$, −45 °C, then Me_2S, (99%).

allowing for a highly regioselective Diels−Alder process. The second product was the initial Diels−Alder adduct **18** (i.e., prior to alkene isomerization), which had not been previously observed. This adduct could be isolated and independently converted to alkene **19** by prolonged heating.[16] Oxidation of alkene **19** to allylic alcohol **21** proceeded in high yield but in this case[17] required the use of trifluorodimethyl dioxirane.[18] This is presumably due to the electron-withdrawing Ts group that rendered the olefin less nucleophilic. However, attempts to effect the subsequent chlorination were unsuccessful using a range of chlorinating reagents including NCS, chloramine-T, sodium hypochlorite, 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one, and chlorine gas. The major product isolated from these reactions was the aromatized product **23**.[19]

These observations indicate that an electron-withdrawing group on N^1 benefits the regiochemical outcome of the Diels−Alder reaction, while the subsequent chlorination/1,2-shift requires a more electron-rich group on N^1. Generally, this situation would require a protecting group switch. However, we considered the use of an electron-withdrawing group (EWG) that in a subsequent transformation could be converted to a more electron-rich group. In this regard, we envisioned the use of a tosylvinyl (Tsv) group[20] that, in a vinylogous manner, would approximate the electron-withdrawing nature of a tosyl group essential for a regioselective Diels−Alder reaction (Scheme 3). Subsequent olefin

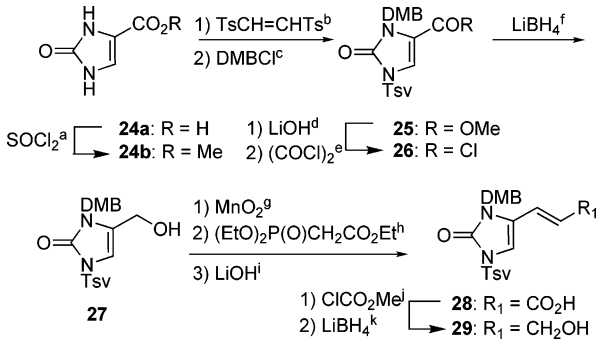
Scheme 3. Tsv Group as an Electronically Adjustable Nitrogen Protecting Group



reduction would yield a tosylethyl (Tse) protecting group[21] that would serve as a more electron-rich group determined to be necessary for the chlorination/ring contraction sequence. One concern in this strategy was the possibility that the Tsv group would participate as a dienophile.

Synthesis of the required diene **29** began with the methyl ester **24b** obtained by methylation of the known imidazolone **24a** (Scheme 4).[2a] (*Z*)-1,2-Di-*p*-toluenesulfonylethylene[22] was

Scheme 4. Synthesis of the Tsv-Protected Diene[a]



[a] Reagents and conditions: (a) MeOH (60%); (b) NaH, DMF, 20 °C, 15 h; (c) K_2CO_3, DMF, 60 °C, (56% over two steps); (d) THF/H_2O, 20 °C; (e) THF, cat. DMF, 25 °C; (f) THF, −78 °C (96% over three steps); (g) CH_2Cl_2, 25 °C (82%); (h) THF, NaH; (i) THF/H_2O (3/1, v/v), 20 °C; (j) THF, Et_3N, 0 °C; (k) THF, −78 °C (77% over four steps).

used to install the Tsv group at the more accessible nitrogen (N^1) via a presumed addition−elimination (-Ts) process. Protection of N^2 with DMB chloride gave the bis-protected imidazolone ester **25** in 56% overall yield for the two steps. Attempts to selectively reduce ester **25** to alcohol **27** using DIBALH were unsuccessful leading to concomitant reduction of the Tsv alkene. A more lengthy but high-yielding sequence

(16) Lovely has observed related alkene isomers in similar Diels−Alder reactions employing vinyl imidazoles (see ref 9a).

(17) Oxidation of the dibenzylated adduct **14** could be achieved in nearly quantitative yield with dimethyl dioxirane (see ref 2a).

(18) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890.

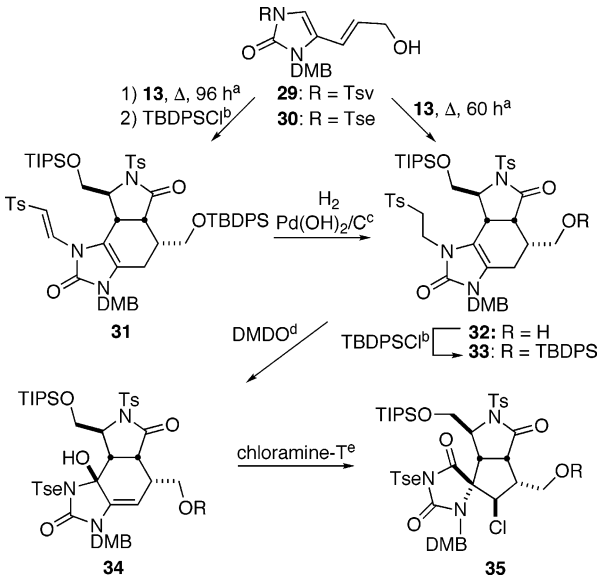
(19) Since this 1,2-shift proceeds through an electron-poor, three-centered, two electron transition state, it appears that elimination processes leading to aromatized product **23** become competitive with the desired 1,2-shift.

(20) To the best of our knowledge, the use of the Tsv group as a protecting group has not been described in the literature.

involving hydrolysis to the acid, acid chloride formation, and reduction with lithium borohydride gave alcohol **27** in 96% overall yield for the three steps. Oxidation proceeded smoothly to give the corresponding aldehyde in 82% yield. Following olefination, a three-step sequence was again required to prevent reduction of the Tsv group. Horner−Wadsworth olefination, hydrolysis of the ester, mixed anhydride formation, and treatment with $LiBH_4$ provided dienyl alcohol **29** in 77% yield over the four steps. The synthesis of diene **29** is lengthy but requires no purification by column chromatography throughout the 10-step sequence from ester **24b**. Instead, acid−base extractions were used to purify the intermediate carboxylic acids.

Heating diene **29** with dienophile **13** in benzene in a sealed tube at 95 °C *pleasingly led to the formation of a single regioisomeric, Diels−Alder adduct **31*** in 48% overall yield following protection of the alcohol as the TBDPS ether (Scheme 5). Similar results were obtained using microwave

Scheme 5. Diels−Alder Reactions and the Oxidation/Chlorination/Rearrangement Process[a]



[a] Reagents and conditions: (a) 2,6-lut, 95 °C, sealed tube; (b) Et_3N, DMAP, CH_2Cl_2, 24 h, 25 °C (48% of **33** based on **13**, 2 steps; 48% of **31** based on **13**, 2 steps); (c) EtOAc, 25 °C (93%); (d) CH_2Cl_2, −50 °C; DMS (99%); (e) CH_2Cl_2, −50 → 25 °C (65%).

irradiation at 175 °C for 45 min. In agreement with previous studies, the double bond had isomerized to regenerate the imidazolone ring under the reaction conditions. An additional product isolated was tentatively assigned the structure resulting from competing dimerization of the diene in which the Tsv group had served as a dienophile. Selective reduction of the Tsv olefin of tricycle **31** was readily accomplished by hydrogenation to yield the Tse-protected adduct **33** in near-quantitative yield. Corroboration of this structure was obtained by independent synthesis of the same Diels−Alder adduct from the Tse-protected diene **30**[23] and subsequent alcohol protection. Comparison by ^1H and ^{13}C NMR verified that the same cycloadduct had been obtained by the two routes.

A two-stage oxidation/rearrangement as described previously[2a] provided the cyclopentane **35**. Oxidation of the Tse-protected Diels−Alder adduct **33** provided the allylic alcohol **34** in nearly quantitative yield. Subsequent treatment with NCS resulted in the formation of the aromatized product (cf. **23**) as the major product. However, treatment with chloramine-T at low temperature minimized formation of the aromatized product providing cyclopentane **35** as the major product.

In summary, strategies leading to improved regioselectivity were designed and implemented for the key Diels−Alder process toward the oroidin alkaloids axinellamine and palau'amine. One strategy entailed the use of an electronically adjustable protecting group to circumvent the need for a cumbersome and potentially difficult protecting group switch. While the efficiency of the Diels−Alder process using the Tsv-protected diene is not fully optimized, we anticipate that the concept of an electronically adjustable protecting group may find wider application in organic synthesis. The advanced spirocyclopentane **35** is a serviceable intermediate in our projected total synthesis of the axinellamines, and the results of these studies will be reported in due course.

Acknowledgment. We thank the NIH (NIGMS 52964), the Welch Foundation (A-1280), and Pfizer for support of these investigations. D.R. is an Alfred P. Sloan Fellow and a Camille Dreyfus Teacher−Scholar. The NSF (CHE-0077917) provided funds for purchase of NMR instrumentation.

Supporting Information Available: Selected experimental procedures and characterization data (including ^1H and ^{13}C NMR spectra) for compounds **17**, **19**, **21**, **25**, **27**, **29**−**31**, **33**, **35**−**40**, **44**, and **47**−**50**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0473602

(21) The Tse group has had limited use; a partial reference list includes: (a) Faubl, H. *Tetrahedron Lett.* **1979**, 491. (b) Gonzalez, C.; Greenhouse, R.; Tallabs, R.; Muchowski, J. M. *Can J. Chem.* **1983**, *61*, 1697. (c) Rao, A. K. S. B.; Rao, C. G.; Singh, B. B. *Synth. Commun.* **1994**, *24*, 341. (d) DiPietro, D.; Borzilleri, R. M.; Weinreb, S. M. *J. Org. Chem.* **1994**, *59*, 5856. (e) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905. (f) Artman, G. D., III; Walman, J. H.; Weinreb, S. M. *Syntheis* **2002**, 2057. (g) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J. *Tetrahedron Lett.* **2002**, *43*, 135. (h) Dastrup, D. M.; Yap, A. H.; Weinreb, S. M.; Henry, J. R.; Lechleiter, A. J. *Tetrahedron* **2004**, *60*, 901 and references cited within.

(22) (a) Snyder, H. R.; Hallada, D. P. *J. Am. Chem. Soc.* **1952**, *74*, 5. (b) Cossu, S.; De Lucchi, O.; Durr, R.; Fabris, F. *Synth. Commun.* **1996**, *26*, 211.

(23) This diene was prepared by an analogous procedure as for diene **17** employing the mesylate of β-tosylethanol for N^1 protection (see the Supporting Information for details). This diene provided a 2.5:1 ratio of Diels−Alder regioisomers, with the major product being the desired regioisomer.