HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 143 - 154. © The Japan Institute of Heterocyclic Chemistry
Received, 29th January, 2008, Accepted, 18th February, 2008, Published online, 22nd February, 2008. COM-08-S(N)15

ASYMMETRIC SYNTHESIS OF THE ABCD RING SYSTEM OF DAPHNILACTONE B *VIA* A TANDEM, DOUBLE INTRAMOLECULAR, [4+2]/[3+2] CYCLOADDITION STRATEGY†

Scott E. Denmark,* Son T. Nguyen, and Ramil Y. Baiazitov

Department of Chemistry, Roger Adams Laboratory,
University of Illinois, Urbana, Illinois 61801, USA
denmark@scs.uiuc.edu

Abstract - An asymmetric synthesis of the ABCD ring system of daphnilactone B is described. The synthesis features a tandem, double intramolecular, [4+2]/[3+2] cycloaddition of a highly functionalized, enantiomerically enriched nitroalkene to generate a pentacyclic nitroso acetal. The cycloaddition establishes six contiguous stereogenic centers including the critical CD ring junction that bears two quaternary stereogenic centers. Hydrogenolysis of the nitroso acetal followed by amide reduction and cyclization provided the AB rings. The methyl substituent on the A ring was installed in the correct configuration *via* hydrogenation of an exocyclic olefin in the final step.

The *daphniphyllum* alkaloids are a family of polycyclic, squalene-derived amines that have been isolated from trees of the genus *Daphniphyllaceae*.[1] Since the first member of this family, yuzurimine, was isolated in 1966,[2] over 100 members have subsequently been discovered. Among these, daphnilactone B was isolated from the fruits of *Daphniphyllum teijsmanni* Zollinger in Japan in 1972.[3] The structure of daphnilactone B was determined by spectroscopic analysis, chemical derivatization and was confirmed by single crystal X-ray analysis (Figure 1).[3b] The absolute configuration of this alkaloid was inferred from correlation to its congeners having known absolute configuration such as daphmacrine,[4] secodaphnilphylline[5] and codaphniphylline.[6] Daphnilactone B possesses a densely fused hexacyclic structure containing seven stereogenic centers, six of which reside in the ABCD domain, including two vicinal quaternary centers. Thus far, no total synthesis of daphnilactone B has been reported. However, elegant syntheses of some structurally related compounds such as (±)-methyl homosecodaphiphyllate,[7]

† This manuscript is dedicated to Prof. Ryoji Noyori on the festive occasion of his 70th birthday and in recognition of his towering achievements in organic chemistry.

(±)-daphnilactone A,[8] and (±)-bukittinggine[9] have been disclosed by Heathcock who devised a brilliant biomimetic strategy.

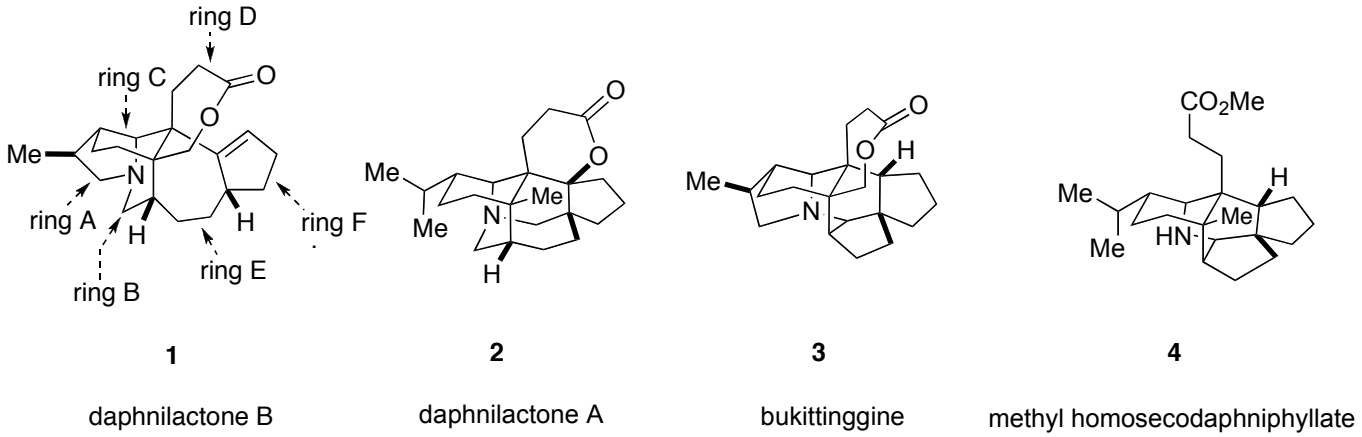
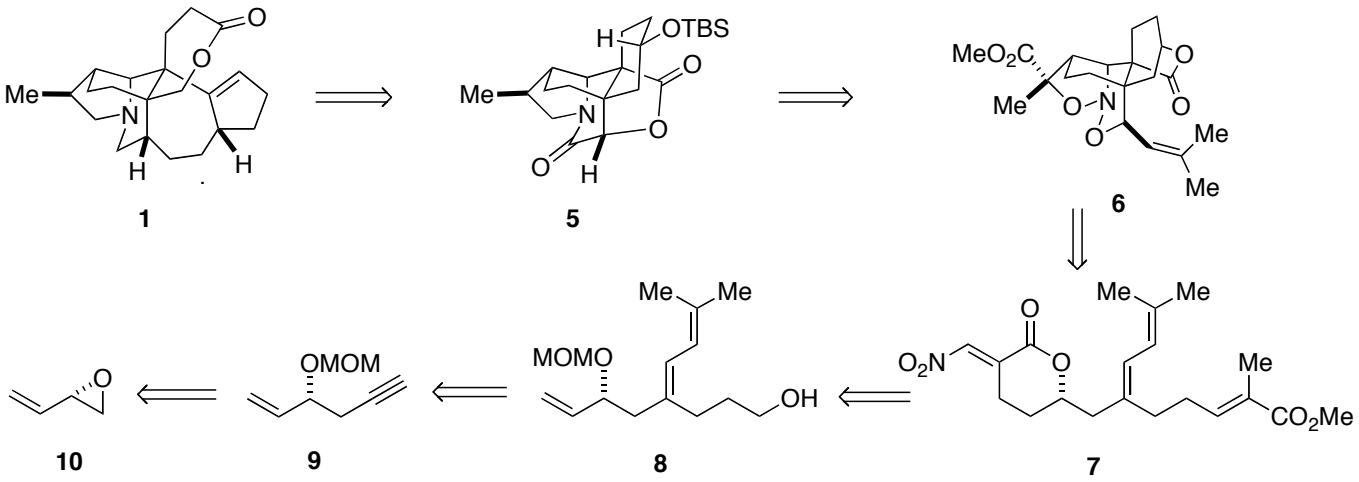


Figure 1. Structures of daphnilactone B and some selected *daphniphyllum* alkaloids.

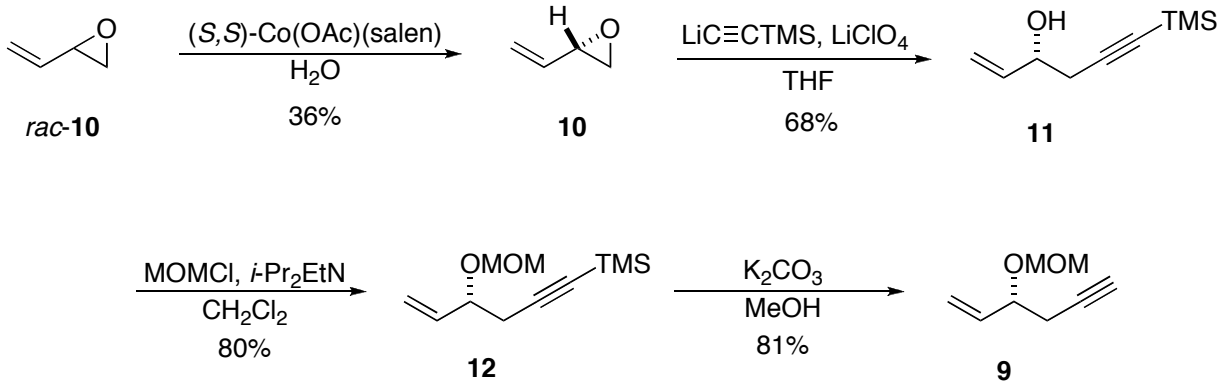
The challenging structure of daphnilactone B was seen as an inspiration to test the viability of the tandem [4+2]/[3+2] cycloaddition of nitroalkenes[10] at the highest level of complexity, namely the *double intramolecular cycloaddition*. It was anticipated that synthesis of the ABCD ring system would illustrate the versatility of nitroalkenes in building molecular complexity by creating multiple bond connections that are not obvious by conventional retrosynthetic analysis. In addition, the work would highlight the effectiveness of the relayed stereoinduction in the double intramolecular cycloaddition process.

The general retrosynthetic analysis for constructing daphnilactone B is summarized in Scheme 1. The key differences of this plan compared to the model studies reported previously[11,12] are: (i) the installation of the primordial stereogenic center in the correct absolute configuration from which all other centers are derived, (ii) the use of an enantiomerically enriched lactone linkage/activator between the nitroalkene and the dipolarophile, and (iii) the introduction of the methyl group in the dipolarophile prior to the tandem cyclization process. We envisioned that the lactone would serve four purposes, it would: (i) dictate the facial selectivity of the [4+2] cycloaddition, (ii) provide latent functionality for the lactone in the D ring, (iii) provide a locus for elaboration of the hydroazulene moiety (the EF rings), and (iv) lower the LUMO of the nitroalkene moiety and thus activate it towards the [4+2] cycloaddition. From the success of previous model studies,[12] alkyne **9** was chosen as the key intermediate. This precursor could be prepared in large quantities from enantiomerically enriched (*S*)-butadiene monoxide and would intersect with the established route to the cycloaddition substrate. From here, the secondary alcohol would become a part of the lactone tether, whereas the alkyne would evolve into the dienophile and dipolarophile units.



Scheme 1

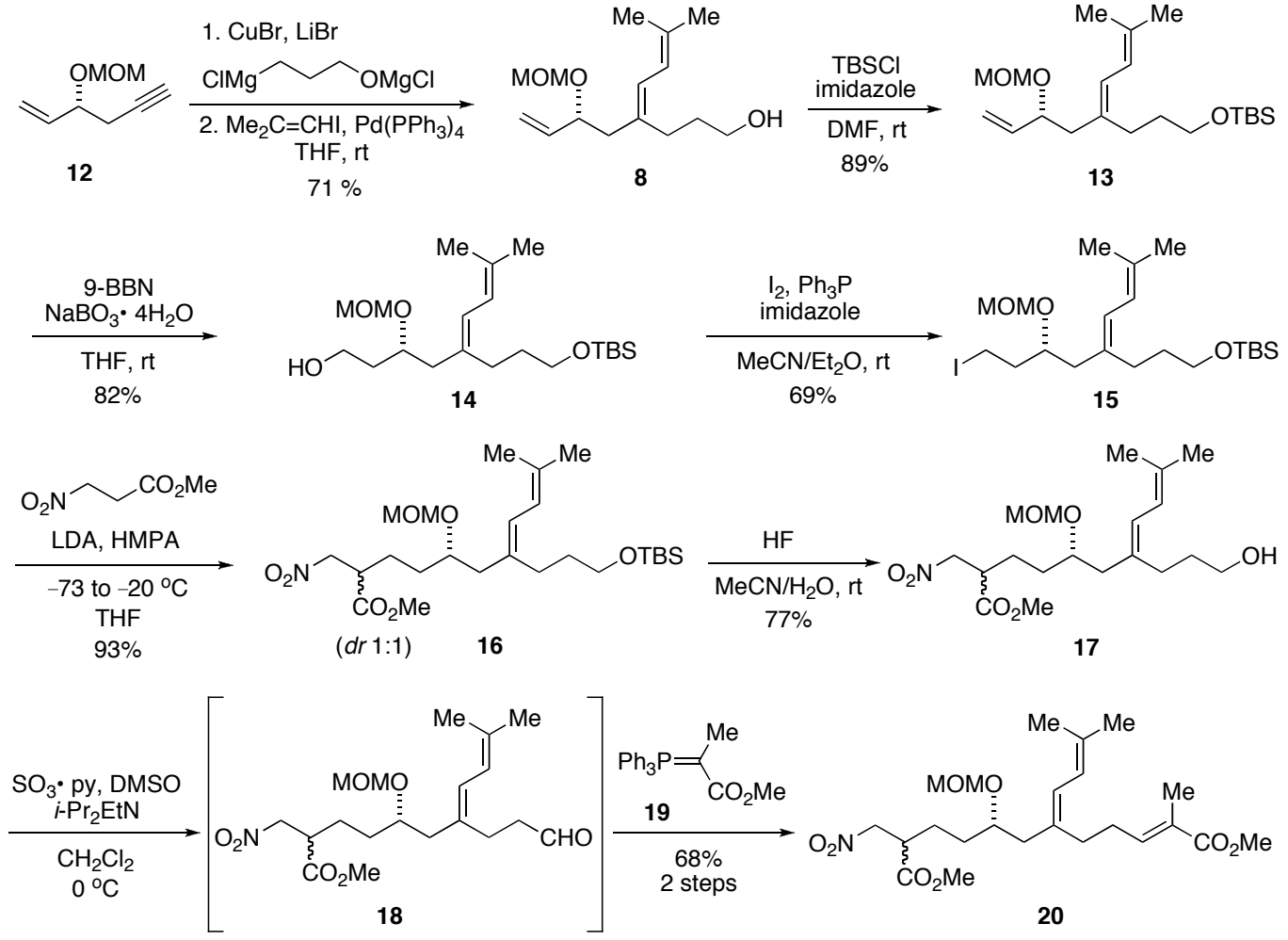
The synthesis began with a hydrolytic kinetic resolution of racemic butadiene monoxide (*rac*-**10**) following method of Jacobsen (Scheme 2).[13] This transformation provided enantioenriched **10** in 36% yield (of a 50% theoretical maximum) with > 99:1 er. The site selectivity in the opening of epoxides has been shown to be dependent on Lewis acid promoters such as $TiCl(O\textit{i}\text{-}Pr)_3$,[14] $BF_3{\cdot}OEt_2$,[15] $LiClO_4$,[16] and Me_3Ga.[17] Reaction of epoxide **10** with lithium trimethylsilylacetylide in the presence of $LiClO_4$ afforded the desired linear product **11** in good yield (68%) with excellent site selectivity (98:2). The secondary alcohol **11** was then protected as a methoxymethyl ether **12** in 80% yield and the trimethylsilyl group was removed with K_2CO_3 to provide the alkyne **9** in 81% yield.



Scheme 2

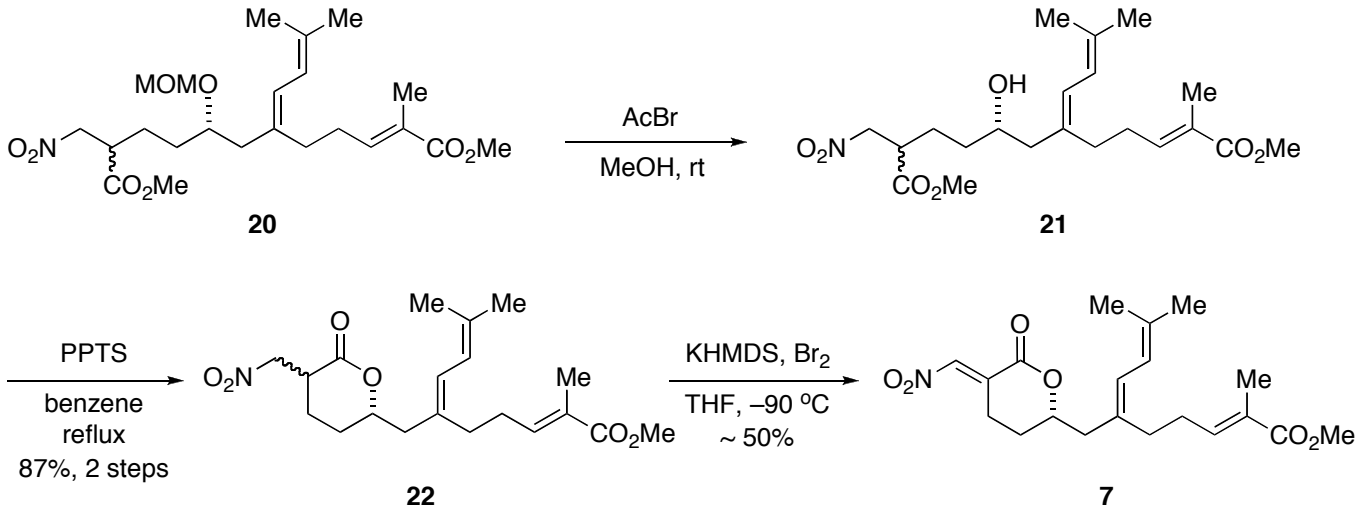
Alkyne **9** was transformed into diene **8** in 71% yield as a single geometrical isomer by use of the previously developed one-pot tandem carbocupration - palladium catalyzed cross-coupling procedure[11] (Scheme 3). The primary alcohol was protected as the *t*-butyldimethylsilyl ether **13** in 89% yield. The

installation of the nitro lactone moiety began with hydroboration of the terminal alkene followed by iodination of the resulting primary alcohol **14** to afford iodide **15** in 57% yield from **13**. The β-nitro carboxylate was introduced *via* alkylation of the dianion generated from methyl-3-nitropropionate[18] with iodide **15**. The reaction is highly efficient, providing **16** in 93% yield as a 1:1 mixture of diastereomers. The diastereomeric mixture of **16** was carried forward as the newly created stereogenic center would eventually become a part of the planar nitroalkene unit. The construction of the dipolarophile began by removal of the *t*-butyldimethylsilyl ether followed by oxidation of the primary alcohol **17** to afford the rather unstable aldehyde **18**. The instability problem was alleviated by employing a one-pot, oxidation - Wittig olefination procedure.[19] In this sequence, the aldehyde was generated *in situ* by the Parikh-Doering oxidation[20] and then was immediately treated with the preformed phosphorane **19**[21] to afford the desired alkene **20** in 68% overall yield (*E*/*Z* ~ 20:1), which contains all of the carbon atoms required for the construction of the ABCD rings.



Scheme 3

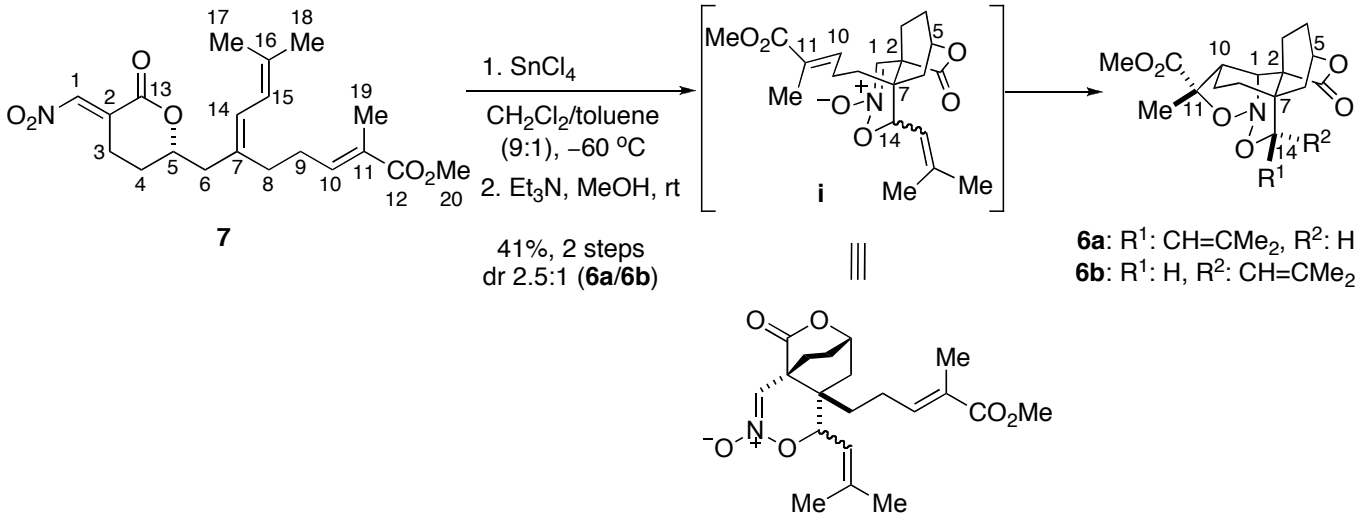
To set the stage for the critical tandem cycloaddition, the lactone tether and the carbon-carbon double bond in the nitroalkene unit needed to be installed. Thus, the methoxymethyl ether in the linear precursor **20** was cleaved with methanolic HBr to provide the alcohol **21** along with **22** (Scheme 4). Subsequent lactonization under mildly acidic conditions smoothly converted the mixture to **22** in 87% yield for the two steps. Dehydrogenation of nitro lactone **22** proved to be quite difficult. After extensive experimentation, the best method found was generation of the nitronate anion by treating the nitroalkane **22** with one equivalent of KHMDS followed by rapid addition of bromine at –90 °C. Upon neutralization and warming the mixture to room temperature, elimination of HBr occurred to provide nitro olefin **7** in moderate yield (~50%, *E*/*Z* ~ 10:1). Nitro olefin **7** could be isolated for characterization by silica gel chromatography. However, to avoid migration of the double bond into the ring as well as the material loss during purification, the crude nitro olefin was used in the next step.



Scheme 4

To effect the tandem [4+2]/[3+2] cycloaddition process, a variety of Lewis acids were surveyed, including $TiCl_4$, $TiCl_3(O\textit{i}\text{-Pr})$, $TiCl_2(O\textit{i}\text{-Pr})_2$, Me_3Al, $MeAlCl_2$, $SnCl_4$, $MeSnCl_3$, BCl_3, $BF_3{\cdot}OEt_2$, Bu_2BOTf, $Zn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Nd(OTf)_3$ (Scheme 5). As anticipated, the [4+2] reaction was difficult because of the highly congested nature of both the 4π and the 2π-components. Relatively mild Lewis acids such as Me_3Al, $TiCl_2(O\textit{i}\text{-Pr})_2$ which served well for a large number of less substituted substrates[22] afforded no conversion whereas, stronger Lewis acids such as $TiCl_4$, or $TiCl_3(O\textit{i}\text{-Pr})$ caused decomposition of the material. Fortunately, $SnCl_4$ (3.0 equiv, CH_2Cl_2, –35 °C) was found to be a suitable Lewis acid for the transformation. Upon neutralization and aqueous workup, the nitronate adduct **i** underwent the [3+2] cycloaddition spontaneously to deliver the final cyclized product **6a**,**b** in ~ 40% (over two steps) from **22** (dr ~1:1). Extensive optimization was undertaken to maximize the

diastereoselectivity for the generation of **6a**. The highest dr (**6a**/**6b**, 2.5:1) was achieved when the reaction was run at –60 °C in a dichloromethane/toluene, 9:1 solvent blend. The selectivity decreases at higher reaction temperatures, longer reaction times or in more polar solvents most likely because of a post-cycloaddition isomerization.[12] For example, at –35 °C, the dr was reduced to 1:1 (48% yield for 2 steps). The structures of **6a** and **6b** were unambiguously confirmed by single crystal X-ray analysis (Figure 2).[23] Overall, this transformation is remarkable in terms of generating molecular complexity: in a single event, four bonds were created to generate four rings and seven stereogenic centers including two quaternary carbons and one pyramidal nitrogen, all with the correct relative configuration with respect to C(5). Notably, the tandem sequence also created a bond between two atoms that were twelve atoms away in the starting material.



Scheme 5

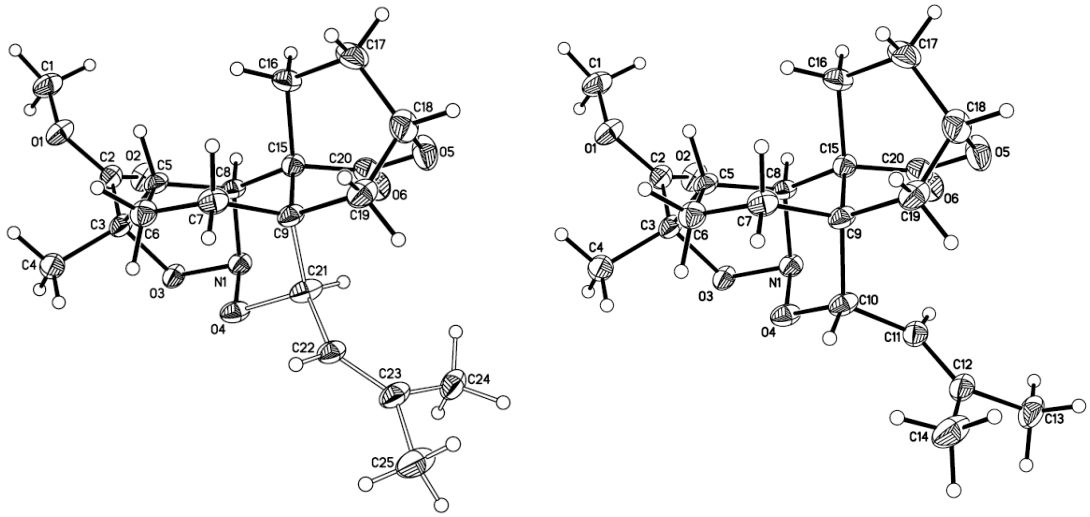
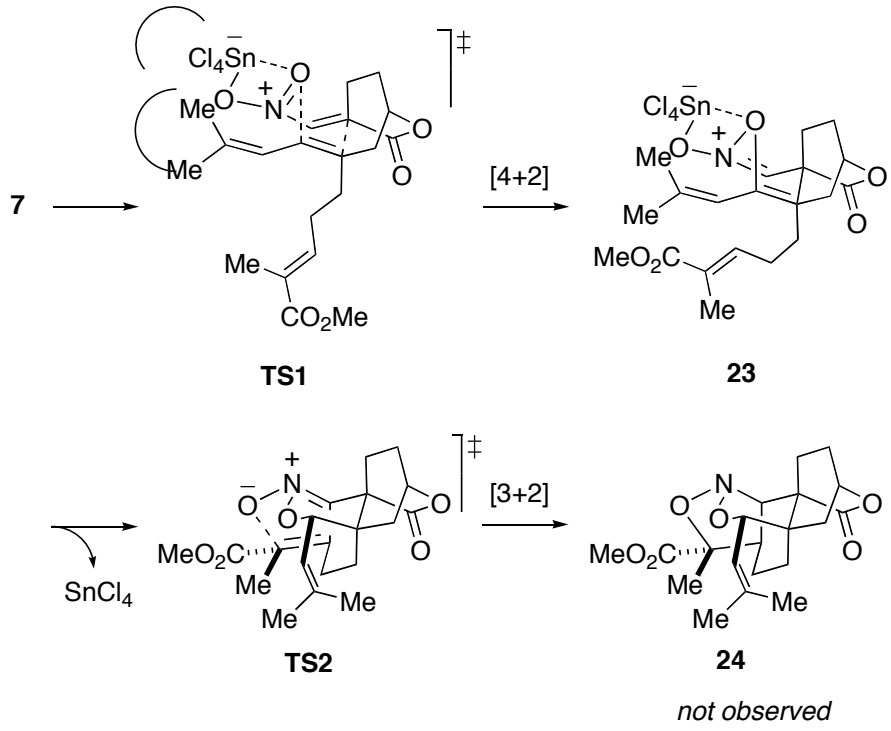


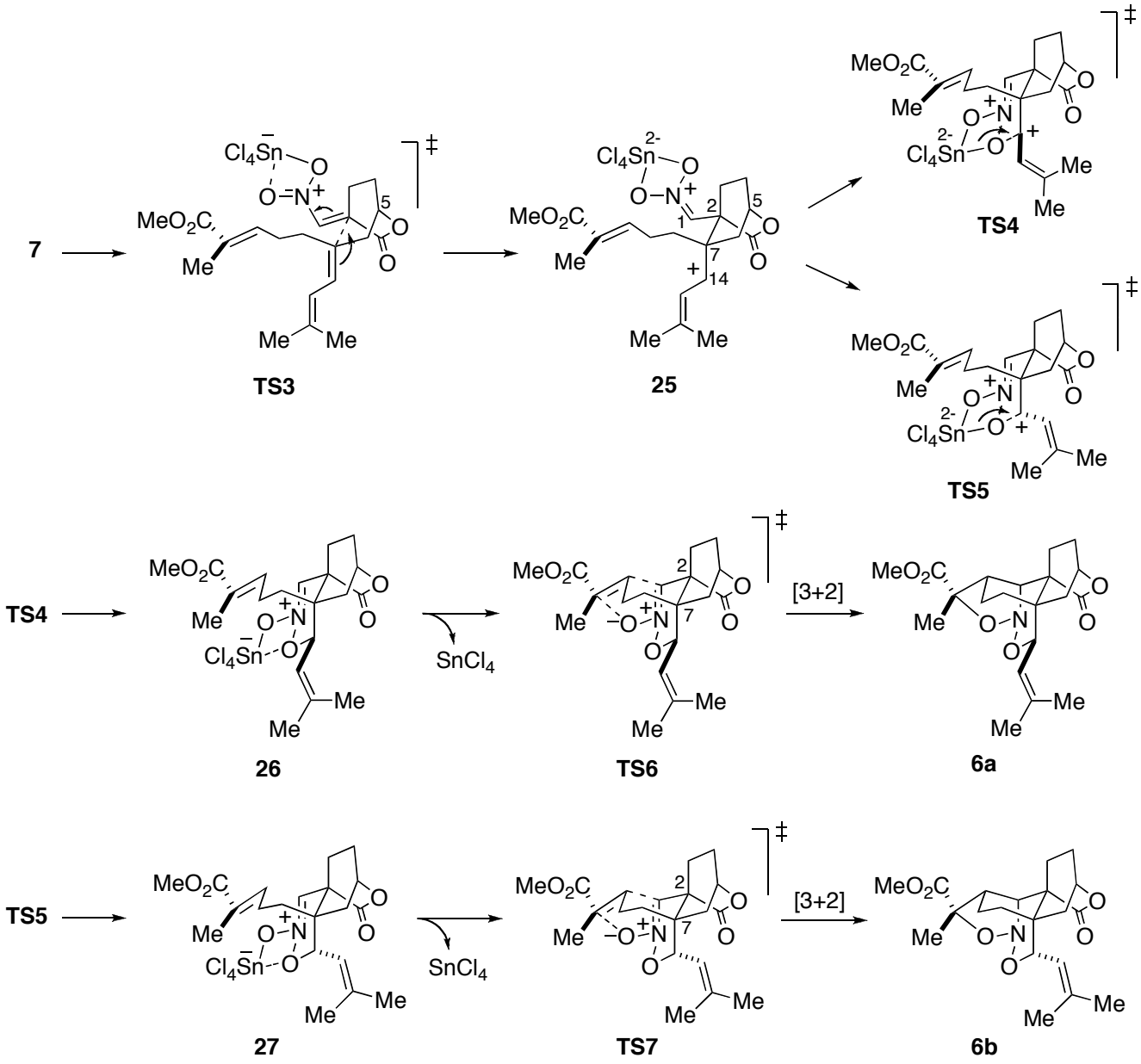
Figure 2. X-Ray crystal structures of **6a** and **6b** (OPTEP images)

The mechanism and stereoselectivity of the transformation merit further comment. Because the nitroalkene in **7** is of *E*-configuration, if the [4+2] and [3+2] reactions are concerted, the final product should be **24** (Scheme 6). The fact that this product was not observed most likely arises from the severe steric interaction between the prenyl group and the $SnCl_4$-bound nitro group in the hypothetical boat-boat transition structure (**TS1**).



Scheme 6

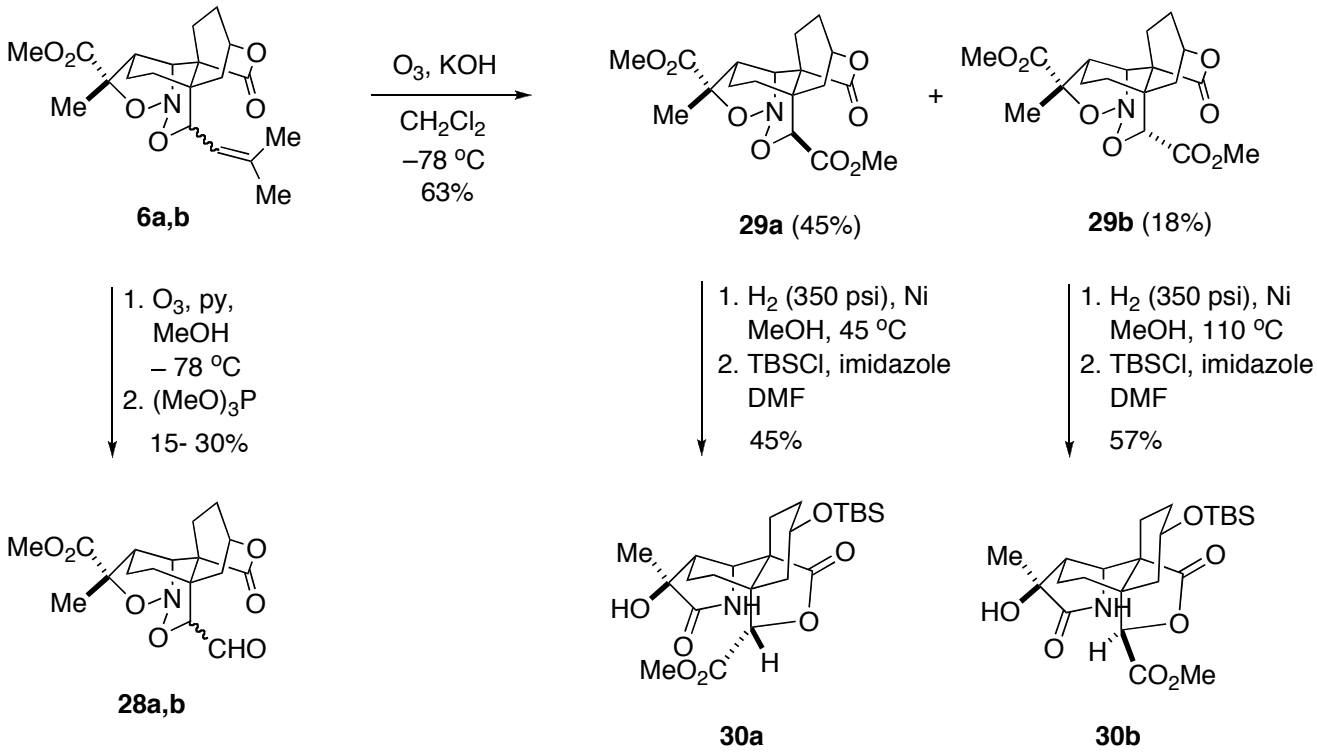
To explain the formation of products **6a,b** we propose that the [4+2] reaction proceeds *via* a stepwise mechanism (Scheme 7).[12] In the event, the intramolecular attack of the conjugated alkene on the Lewis acid-activated nitroalkene moiety results in the formation of two quaternary carbon centers. The facial selectivity of the attack is controlled by the preexisting stereogenic center C(5) in the lactone tether (**TS3**). To complete the formal [4+2] process, the nitronate moiety in **25** must rotate around the C(1)-C(2) single bond to reach the allylic cation. At that moment of the attack, if the allylic cation possesses its original conformation (**TS4**), the adduct will be the intermediate **26**. On the other hand, if the allylic cation reacts *via* a conformation resulting from 180° rotation around the C(7)-C(14) (**TS5**), the adduct will be **27**. Regarding the [3+2] process, the facial selectivity of the dipolarophile addition to the nitronate intermediate is controlled by the two newly created C(2)-C(7) stereogenic centers, whereas the relative configuration is dictated by the *E*-configuration of the dipolarophile olefin and the tether length. The stereospecificity of the [3+2] process is consistent with a concerted mechanism for this step.



Scheme 7

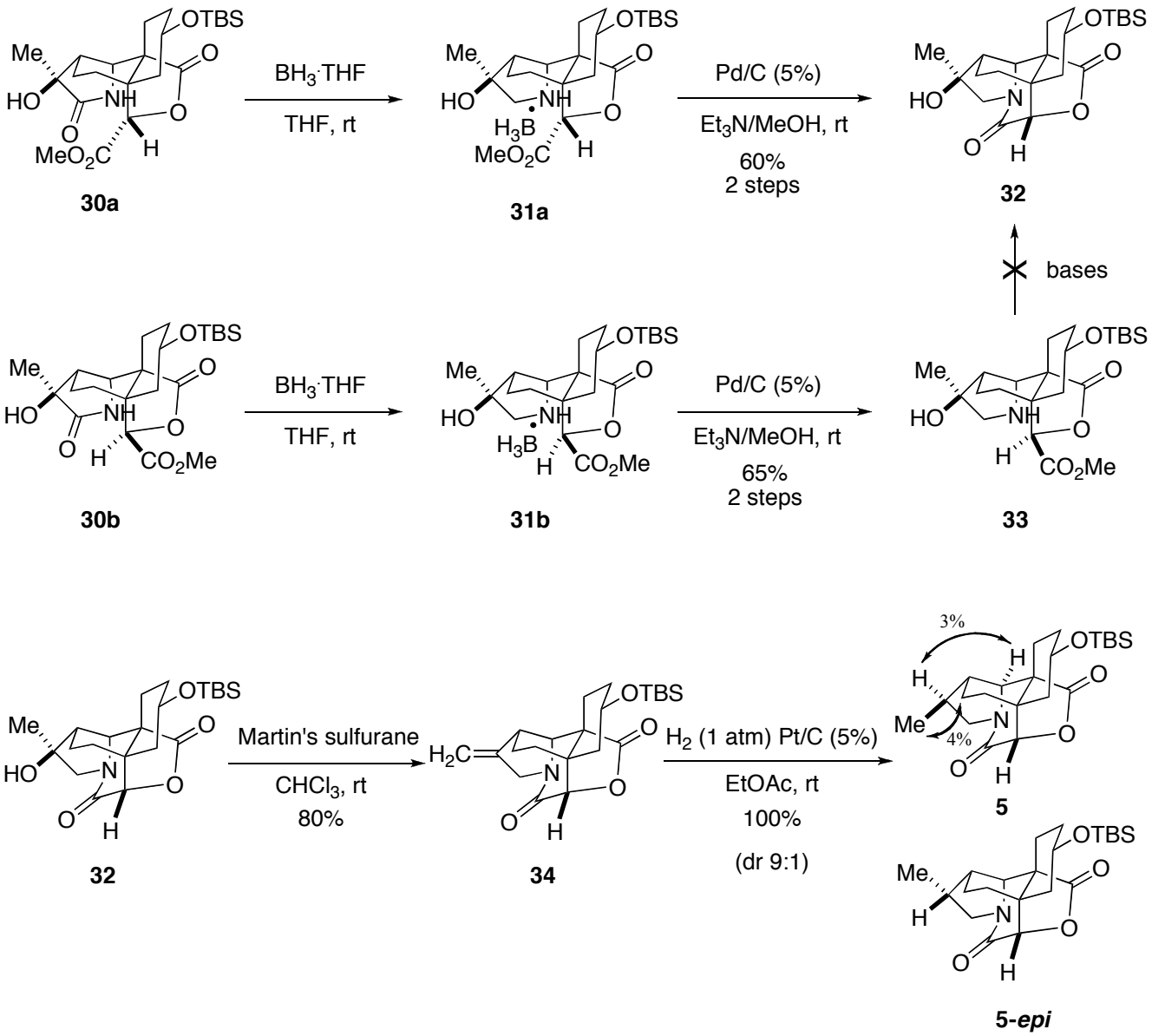
With the pentacyclic nitroso acetals **6a,b** in hand, the next goal was to form the AB rings. Unfortunately, ozonolysis of the prenyl moiety in **6a**,**b** under standard conditions[11] resulted in low and inconsistent yields of the corresponding aldehydes **28a**,**b** (Scheme 8). Apparently, the proximal carbonyl oxygen of the lactone interferes with this process. To circumvent this issue, Marshall's procedure was employed to convert the alkene to the corresponding carboxylic ester **29a**,**b** by treatment with ozone in presence of potassium hydroxide (in 63% yield).[24] The two epimers **29a** and **29b** were separated by silica gel chromatography because the successful hydrogenolyses of **29a** and **29b** required that they be carried out at different reaction temperatures. In these reactions, the nitroso acetals are first reduced to the corresponding amino diols. The amino group in each nitroso acetal then reacts further with the proximal

methyl ester to form a five-membered lactam (ring A). Subsequently, the secondary alcohol participates in a translactonization with the six-membered lactone to form a thermodynamically more favored five-membered lactone. The products of the hydrogenolyses were very polar and difficult to purify. Thus, the crude products were converted to the *t*-butyldimethylsilyl ethers**,** which were purified easily to provide **30a** and **30b** in 45% and 57% yields.



Scheme 8

Separate reduction of the lactam function in **30a** and **30b** with BH_3·THF furnished the amine-borane complexes **31a** and **31b** (Scheme 9). Treatment of the complex **31a** with 5% Pd/C in methanol cleanly removed the borane to reveal the free amine[25] which underwent subsequent lactamization to provide the desired lactam **32**. Under the same conditions, the complex **31b** provided the amine **33** which could not be converted to **32,** despite many attempts at enolization/cyclization under various basic conditions.[26] To complete the synthesis of **5**, tertiary alcohol **32** was treated with Martin's sulfurane[27] to afford alkene **34** in 80% yield. The final step of the sequence was the installation of the methyl group by saturation of the olefin. Hydrogenation of **34** at 1 atm H_2 with Pt/C (5%) provided compound **5** along with 10% of its epimer.[11] For the same transformation, Wilkinson catalyst gave only 4:1 diastereomeric mixture (favoring **5**). The configuration of the methyl bearing stereogenic center of the major component was determined by NOE correlations. The selectivity of the hydrogenation can be rationalized by the preferred approach of the convex face of the ring system to the platinum surface to avoid the steric bulk of the BC rings.



Scheme 9

In summary, the pentacyclic compound **5** bearing the ABCD ring system of the daphnilactone B has been synthesized in 22 steps, 0.36% overall yield starting from (*S*)-butadiene monoxide. The synthesis features an efficient tandem, double intramolecular, [4+2]/[3+2] cycloaddition based on the Lewis acid activated nitroalkene platform. The high (internal) diastereoselectivity of the tandem cycloaddition allowed for the installation of six contiguous stereocenters in **6** with respect to the single stereogenic center derived from (*S*)-butadiene monoxide. This work lays a solid foundation for an asymmetric total synthesis of (–)-daphnilactone B.

ACKNOWLEDGEMENTS

We are grateful for the National Institutes of Health (GM30938) for generous financial support. R.Y.B. thanks the Alumni Donors of the Chemistry Trust of UIUC, Abbott Laboratories and Johnson & Johnson Pharmaceutical Research Institute for graduate fellowships.

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23. These nitroso acetals could not be separated by chromatography. A crystal was obtained that had a roughly 5:1 composition of the diastereomers favoring **6b**. The X-ray crystallographic solution converged on a structural model represented by both isomers in the crystal. The crystallographic coordinates of **6a** and **6b** have been deposited with the Cambridge Crystallographic Data Centre; deposition No. 675071. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; via www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk.
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26. The different behavior of **29a**/**29b** and **31a**/**31b** highlights the importance of maximizing the diastereoselectivity of the tandem cycloaddition. Other opportunities for the conversion of **33** to a pentacyclic lactam will be investigated, including selective lactone opening.
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