DOI: 10.1002/chem.200801161

Assessing Synthetic Strategies: Total Syntheses of (±)-Neodolabellane-Type Diterpenoids

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Abstract: Two strategies, namely a cross-metathesis/ring-closing metathesis and Pd-catalyzed Stille allylation/Nozaki–Hiyama–Kishi coupling, are examined for the preparation of neodolabellane-type diterpenoids **1** and **2**. Whereas the first approach possessed synthetic limitations, the latter was successfully employed to provide compounds **1** and **2** in 8.8% (14 steps) and 8% (15 steps) overall yields, respectively.

Keywords: macrocyclization · metathesis · neodolabellane · palladium

Introduction

Dolabellanes, and their relatively rare neodolabellane analogues, are a class of bicyclic diterpenes comprised of an 11-membered macrocycle fused to a cyclopentyl moiety. Whereas dolabellanes are isolated from marine and terrestrial sources alike, neodolabellanes are to date exclusively of marine origin, specifically corals.[1] Their proposed biosynthesis is initiated with a metal-cation-based enzymatic ionization of geranylgeranyl diphosphate (Figure 1). A double-cascade cyclization provides the dolabellane scaffold, followed by a series of [1,2]-sigmatropic rearrangements to give the corresponding neodolabellane. In addition to their intriguing and varied structures, their cytotoxic, antibacterial, antifungal, antiviral, antimalarial, molluscicidal, ichthyotoxic and phytotoxic activities have made them the aim of many recent formal and total syntheses. Corey and co-workers have recently established a program to develop efficient strategies for the synthesis of these natural products.[2]

Mehta and co-workers reported the first total synthesis of a dolabellane diterpenoid in 1990.[3] They prepared (−)-δ-araneosene using as their key step an oxy-Cope-induced four-carbon annulative ring expansion to generate the dolabellane skeleton. Since then, most synthetic routes leading to dolabellanes involve macrocyclization via intramolecular

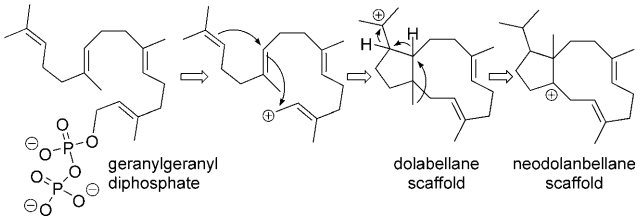

Figure 1. Proposed biosynthesis of dolabellanes and neodolabellanes.

alkylations following in situ deprotonation of cyanohydrins,[4] β-ketoesters,[5] phosphonates (Horner–Wadsworth–Emmons reaction)[6] and sulfones (Julia condensation).[7] Using either D-mannitol or L-ascorbic acid as a chiral starting material, Yamada has published five total syntheses relying on such alkylation methodology, although 35 steps or more were required for each.[6,7a,c] Corey and co-workers have developed several efficient routes relying on ring expansion and/or contractions to obtain the desired fused bicyclic framework. These include reductive pinacol couplings followed by either a dianion-accelerated oxycope rearrangement[8] or pinacol rearrangement.[2] An enantioselective Claisen rearrangement[9] and a Diels–Alder macrobicyclization followed by a ring contraction[10] have also been used. In total, their group has realized eight total syntheses of six dolabellanes, all of which use derivatives of *trans,trans*-farnesol as building blocks that are preset with the two requisite macrocycle *E*-trisubtituted olefins.

To date, 17 total syntheses of 11 dolabellanes have been reported. However, presumably a consequence of their rarity in nature, there exist only two total syntheses of neodolabellanes, both of which were accomplished by Williams and co-workers. They have employed both a Julia condensa-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801161.

tion[7d] and a reductive pinacol coupling[11] to close the 11-membered macrocycle, the latter synthesis being the most highly convergent approach for the preparation of these molecules to date. We became interested in not only increasing the number of synthetically prepared neodolabellanes but, more importantly, expanding the methodology for the macrocyclization of this molecule class. As such, we sought out to prepare neodolabellane-type diterpenoids **1** and **2** whose structures were reported in 2004 after being isolated from the Okinawan soft coral *C. koellikeri*.[12] Although compound **2** was not subjected to biological assays, compound **1** was shown to possess in vitro growth inhibition against various cancer cell lines.[13]

We envisaged two possible routes for the preparation of **1** and **2** (Figure 2), both relying on the manipulation of the macrocyclic olefins to achieve macrocyclization, either by ring-closing metathesis (RCM)[14] or Nozaki–Hiyama–Kishi (NHK) coupling.[15] Although in the latter case the olefin geometry is pre-defined, it has been shown possible to manipulate the *E*/*Z* selectivity in the RCM of 11-membered rings.[16] Following the retrosynthesis from disconnection **A**, a cross-metathesis[17] of **5** with **4** would realize the *E*-trisubstituted olefin[18] as the first key step. The retrosynthesis from disconnection **B** relies on the Pd-catalyzed allylation of a vinyl stannane as the first key step. Both proposed routes are relatively efficient, and stem from copper-catalyzed conjugate addition to commercially-available 2-methyl-2-cyclopenten-1-one (**6**) to set the necessary relative stereochemistry on the five-membered ring.[11,19]

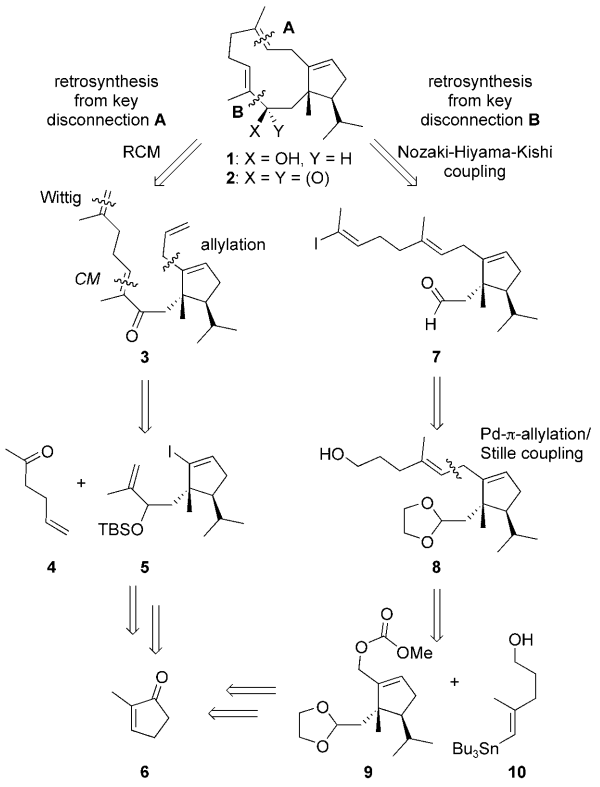


Figure 2. Retrosynthetic analyses of **1** and **2**.

Results and Discussion

Synthesis from disconnection A: The cross-metathesis approach

In order to assess the feasibility of the cross-metathesis reaction, we opted to first carry out a model study in which compound **12**, prepared in only two steps, would act as a surrogate to advanced intermediate **11** (Figure 3). The "metathesis site" of both molecules is identical, with the assumption that the distal cyclic moieties will have little effect on the cross-metathesis.

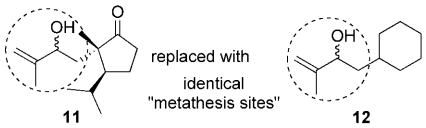
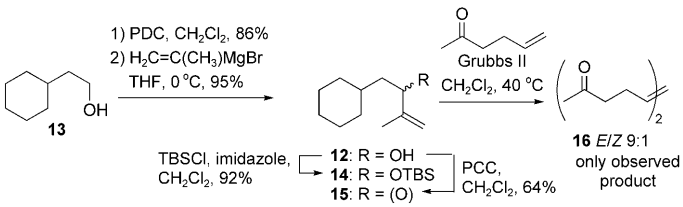


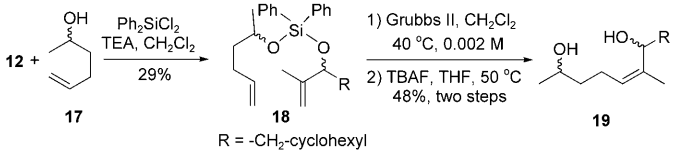
Figure 3. Compound **12** as a surrogate for compound **11** in the cross-metathesis model study.

Oxidation of commercially available 2-cyclohexylethanol (**13**) with PDC followed by addition of isopropenylmagnesium bromide to the intermediate aldehyde provided allylic alcohol **12** (Scheme 1). Silylation with TBDMSCl or oxidation with PCC provided compounds **14** and **15**, respectively. Unfortunately, cross-metathesis of **12**, **14**, or **15** with 5-hexen-2-one using Grubbs second-generation N-heterocyclic carbene–Ru catalyst provided homodimer **16** as the only product.



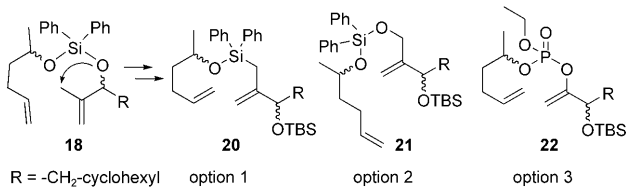
Scheme 1. PDC = pyridinium dichromate, TBSCl = *tert*-butyldimethylsilyl chloride, PCC = pyridinium chlorochromate.

Given the predisposition of cross-metathesis toward less sterically hindered olefins, we opted to join the two fragments via a temporary silicon tether to give silaketal **18** via addition of Ph_2SiCl_2 to an equimolar mixture of alcohols **12** and **17** (Scheme 2).[20] The now intramolecular ring-closing metathesis proceeded under dilute reaction conditions to give diol **19** after fluoride-induced cleavage of the silicon tether. Although establishing proof-of-concept, the requisite *E* geometry of the trisubstituted olefin is energetically disfavored when forming nine-membered rings. As such, we explored relocating the anchor site for the tether in compound **12**.

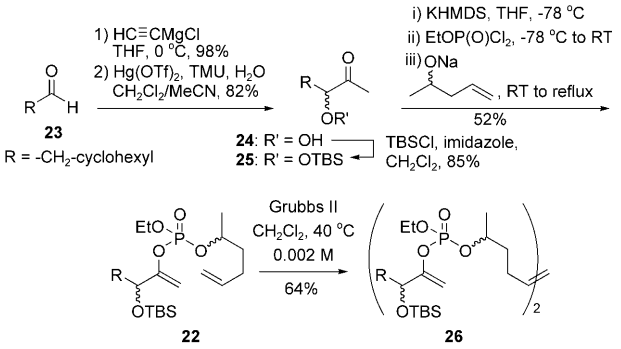


Scheme 2. TEA = Triethylamine.

The required vinyl methyl moiety in compound **18** prejudiced our choices to three options. Allylsilane **20** (option 1) and allyl ether **21** (option 2) possess synthetic challenges in



terms of tether detachment post-RCM, namely olefin migration and deoxygenation, respectively. Replacing the silicon tether with a vinyl phosphate tether (**22**, option 3) offers the intriguing possibility of installing the methyl moiety after RCM via Ni-mediated cross-coupling of the vinyl phosphate, a pseudo-halide, with MeMgBr.[21] We therefore explored the preparation of phosphate **22** (Scheme 3).

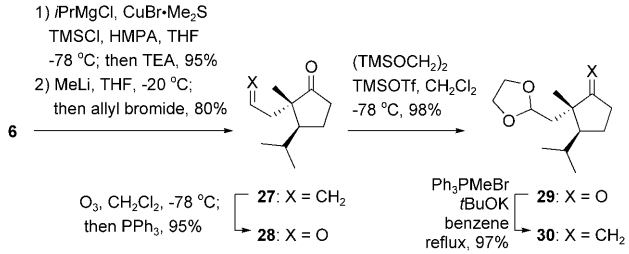


Scheme 3. TMU = *N*,*N*,*N*,*N*-Tetramethylurea.

Ethynylmagnesium chloride addition to aldehyde **23** followed by mercuric triflate/*N*,*N*,*N*,*N*-tetramethylurea-catalyzed hydration[22] of the propargylic alcohol effectively provided α-hydroxy methyl ketone **24**. Silylation of **24** with TBDMSCl proceeded as expected to yield **25**. The kinetic potassium enolate of **25** was quenched chemoselectively with ethyl dichlorophosphate, followed by addition of the sodium alkoxide of racemic 5-hexen-2-ol (preformed) to provide **22**. Despite reports of successful RCM with vinyl ethers,[23] cross-metathesis providing homodimer **26** was predominate in our case, the mass balance being comprised of a complex mixture of unidentified compounds. The combination of results thus far obtained for the first key step of retrosynthesis A prompted us to switch focus to retrosynthesis B for the preparation of diterpenoids **1** and **2**.

Synthesis from disconnection B: The π-allyl substitution/NHK coupling approach

Following Pier's protocol,[19b] TMSCl/HMPA-accelerated copper-catalyzed conjugate addition[24] of isopropylmagnesium chloride to 2-methyl-2-cyclopenten-1-one (**6**) followed by lithium enolate capture with allyl bromide provided racemic **27** in good overall yield (Scheme 4).[25] This procedure was later expanded on by Williams and co-workers to give ketoaldehyde **28** after ozonolysis.[11] Chemoselective protection of the aldehyde in the presence of the hindered neopentyl ketone was achieved using Noyori's conditions to provide **29**;[26] exocyclic olefin **30** was prepared subsequently via one-carbon homologation of **29**.



Scheme 4. HMPA = hexamethylphosphoric triamide.

We envisioned several routes to manipulate either **27**, **29** or **30** to the corresponding allylic alcohol or a derivative thereof (Figure 4).

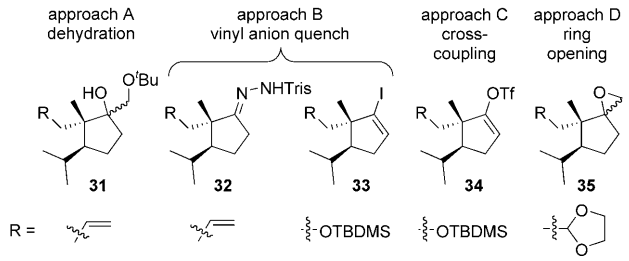


Figure 4. Possible intermediates en route to the corresponding allylic alcohols or derivatives thereof.

- *Approach A*: Elimination of the tertiary alcohol **31** would provide access the corresponding *tert*-butylallyl ether, however, addition of *tert*-butoxymethyllithium[27] or the less basic *tert*-butoxymethylcerium chloride[28] to ketone **27** was unsuccessful, presumably a consequence of preferred enolization.
- *Approach B*: Formation of the vinyl anion is possible via either the Shapiro reaction[29] or lithium–iodide exchange. Treatment of the trisylhydrazone[30] **32** with *s*BuLi and quenching the intermediate vinyl lithium species with

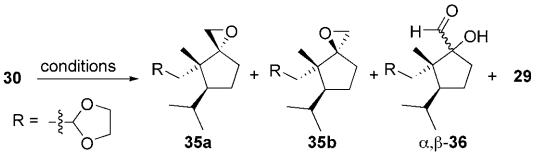
suitable electrophiles (e.g. DMF or methyl chloroformate) provided the corresponding products in a maximum 38% yield. Conversely, lithium–iodide exchange of the vinyl iodide **33** and quenching with methyl chloroformate provided the α,β-unsaturated ester in 70% yield.[31] Although Luche reduction[32] should provide the allylic alcohol, the growing step-count prompted us to explore alternative routes.

- *Approach C*: Williams and co-workers successfully coupled vinyl triflate **34** with Bu_3SnCH_2OH[33] to provide the corresponding allylic alcohol in 67% yield, the mass balance being the protodetriflated species formed via β-hydride elimination of Bu_3SnCH_2OH.[11]
- *Approach D*: An alternative two-step procedure would be to form epoxide **35** from **29** via the Corey–Chaykovsky reaction.[34] Xu and Sun reported on the successful insertion of methylene into a similar neopentyl ketone using the in situ-generated $Me_2S^+CH_2^-$ ylide.[35] However, use of either dimethylsulfonium or dimethyloxosulfonium methylide completely failed in our case. Perhaps the presence of the isopropyl substituent in compound **29** (absent in Xu and Sun's case) forces the five-membered ring into a less reactive conformation. Although warming the reaction could potentially overcome this barrier, the thermal instability of sulfur ylides excludes such an approach. This conjecture is supported by the fact that exocyclic olefin **30** was quantitatively prepared from **29** at 80°C in benzene via the thermally stable phosphonium ylide.

Epoxidation of **30** with 2.5 equivalents of *m*CPBA provided the single diastereoisomer **35a** in addition to α-hydroxyaldehydes α-**36** and β-**36** and ketone **29** (Table 1). Addition of *m*CPBA to purified α,β-**36** gave clean conversion to ketone **29**, substantiating it as an intermediate in the formation of the latter. Conversely, epoxidation with in situ generated dimethyldioxirane[36] provided a 1:2.2 ratio of diastereoisomers **35a** and **35b**, respectively, however, **35b** proved unstable.[37a] In addition, epoxide **35a** was inert to the addition of excess *m*CPBA, whereas **35b** underwent full conversion to ketone **29**.

The observed instability of epoxide **35b** in conjunction with the formation of ketone **29** via intermediate α,β-**36** in

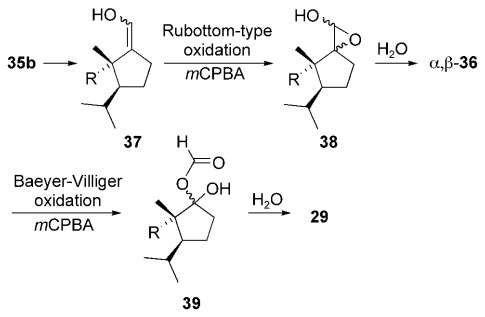
Table 1. Product distribution following the epoxidation of **30** using either *m*CPBA or dimethyldioxirane as the oxidant.



Conditions	**35a**/**35b**/α,β-**36**/**29**
*m*CPBA (82% combined yield)[a]	4.1:0:2.5:1
Oxone, $NaHCO_3$, acetone/water (96% combined yield)[b]	1:2.2:0:0

[a] Ratio determined from isolated yields. [b] Ratio determined by ^{1}H NMR spectroscopy.

the presence of *m*CPBA led us to propose that epoxide **35b** rearranges to give the transient enol **37** in situ[37b] that immediately undergoes Rubottom-type oxidation[38] with a second equivalent of *m*CPBA to provide both observed epimers of **36** via intermediate **38** (Scheme 5). Baeyer–Villiger oxidation to the formate analogue **39** with a third equivalent of *m*CPBA, followed by hydrolysis provides access to ketone **29**.[39] It may be that the initial rearrangement of **35b** to **37** is acid-catalyzed (*m*CPBA $pK_a \approx 7.5$, sold commercially as a mixture with 3-chlorobenzoic acid $pK_a \approx 3.8$)[40] as a similar pathway does not prevail in the presence of dimethyldioxirane.

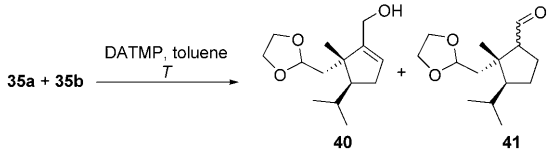


Scheme 5. Proposed pathway for reversion of **35b** to **29**.

Ring opening of the mixture of epoxides **35a** and **35b** using Lewis acids and/or amine bases (e.g. $Al(OiPr)_3$,[41] LDA, TMSI[42] or TMSOTf[43]) proved ineffective. However, in situ generated diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP)[44] cleanly converted a 1:2.2 mixture of epoxides to a ≈1:2.3 mixture of allylic alcohol **40** and aldehyde **41** at both room temperature and −78°C (Table 2, entries 1 and 2). The ratios suggest that different reaction pathways exist for each diastereoisomer. We postulate that the six-membered transition state accessible to the **35a**·DATMP coordination complex leading to allylic alcohol **40** is not available to the **35b**·DATMP complex (Scheme 6).[44,45] As such, the latter undergoes Lewis acid-induced epoxide ring-opening to generate the tertiary carbocation leading to **41** via the diethylaluminum enol ether intermediate. To help substantiate this theory, isolated epoxide **35a** was subjected to the same reaction conditions. At room temperature, a 3.8:1 selectivity in favor of **40** is realized (Table 2, entry 3), suggesting carbocation formation via epoxide ring opening is still a competing pathway, however cooling the reaction to −78°C disfavors this pathway exclusively (Table 2, entry 4).[46]

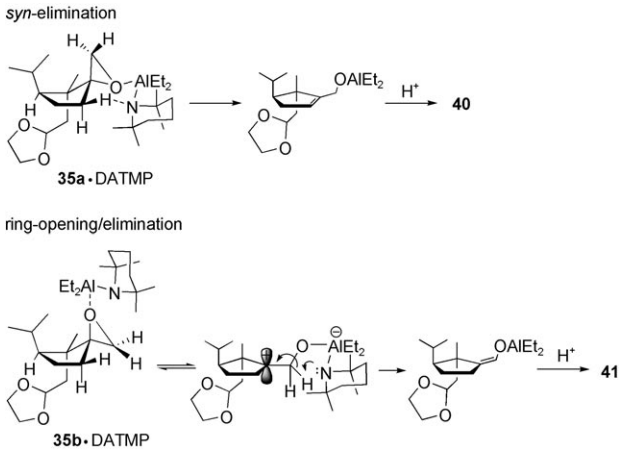
Given the intricacies in the formation, stability and opening of epoxides **35a** and **35b**, we opted to explore another route in preparing the allylic alcohol. Both the endocyclic allylic primary carbonate **9** and the exocyclic allylic secondary carbonate **43** would provide the same Pd–π-allyl complex for cross-coupling. As such, we turned our focus to the preparation of **42** via allylic oxidation (Scheme 7). SeO_2-catalyzed allylic oxidation using *t*BuOOH as a co-oxidant was superior to using stoichiometric amounts of SeO_2 that led to

Table 2. Conditions and ratios of starting materials and product for the epoxide ring opening mediated by DATMP.

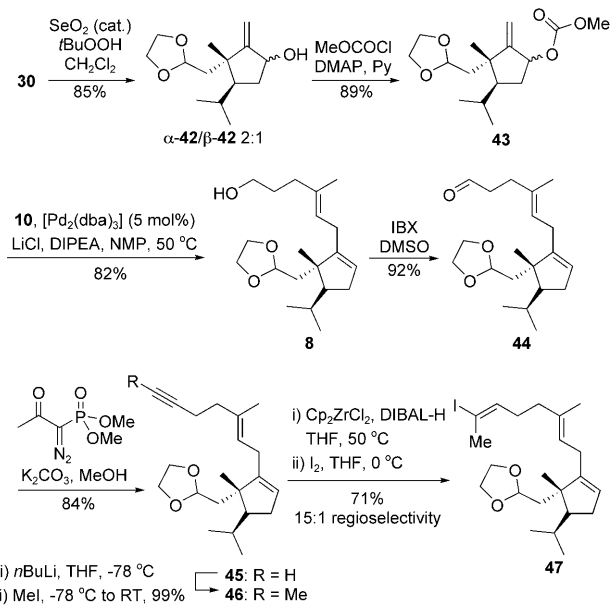


Entry	T	**35a**/**35b**[a]	**40**/**41**[a]
1	RT	1:2.2	1:2.3
2	−78 °C	1:2.2	1:2.3
3	RT	1:0	3.8:1
4	78 °C	1:0	1:0

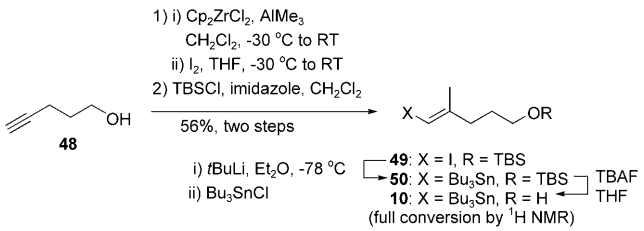
[a] Ratio determined by ^{1}H NMR spectroscopy.



Scheme 6. Proposed mechanism for epoxide **35a** and **35b** ring opening with diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP).



Scheme 7. IBX = 2-Iodoxybenzoic acid.

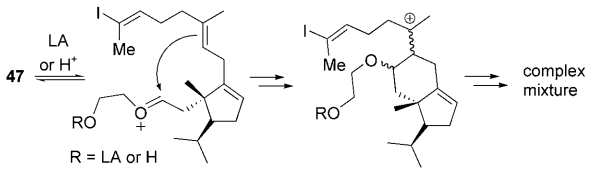


Scheme 8. Preparation of coupling partner **10**.

over-oxidation to the α,β-unsaturated enone.[47] Importantly, this approach provided the required allylic alcohol in a single synthetic step, a considerable advantage over all the routes thus far attempted; subsequent treatment with methyl chloroformate provided **43**.

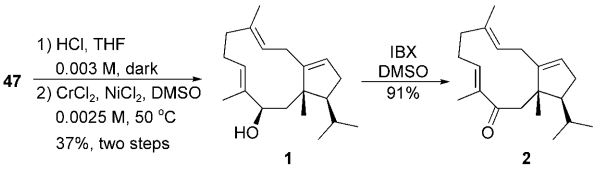
En route to coupling partner **10**, vinyl iodide **49** was prepared via zirconium-mediated methylalumination/iodination of 5-pentyn-1-ol (**48**) followed by TBDMS protection of the primary alcohol (Scheme 8).[48] Lithium–iodine exchange and quenching with tri-*n*-butyltin chloride provided nonpolar vinyl stannane **50** as an inseparable mixture with unidentified organostannane impurities. Silyl cleavage with fluoride provided cross-coupling partner **10** quantitatively.[49] Isolation of the pure compound was not possible due to its decomposition on silica gel, thus the mixture was used directly in the next step without consequence. Regiospecific Pd-catalyzed allylation of **43** with **10** provided **8** followed by oxidation with IBX to give **44** (Scheme 7).[50] One carbon homologation of aldehyde **44** to the terminal alkyne **45** was achieved using the Bestmann–Ohira reagent (Scheme 8).[51] Methylation provided **46** and regioselective hydrozirconation provided the trisubstituted olefin **47** after iodine quench.[52,53]

Conversion of the 1,3-dioxolane **47** to aldehyde **7** proved problematic. An assortment of Brønsted acids (i.e., PPTS, TsOH, acetic acid, HCl),[54] Lewis acids ($InCl_3$,[55] $BiCl_3$[56]) and other reagents (CAN,[57] water/microwave irradiation,[58] thiourea[59]) were examined in a variety of reaction conditions. In all cases, either complete retention or extensive decomposition of **47** was observed. Similar reactivity was observed when subjecting **46** to identical reaction conditions, eliminating the vinyl iodide as the source of the problem. We postulated that either the product aldehyde was not stable in the reaction conditions or that the intermediate oxonium ion was undergoing intramolecular rearrangement to give the tertiary carbocation concomitant with six-membered ring formation, which then further reacts to give the complex mixture of products (Scheme 9). The associated difficulty in the deprotection of unactivated acetals relative to that of ketals and activated acetals (i.e., aryl, benzyl) exacerbates the problem.[54] The product aldehyde **7** was deemed stable to the reaction conditions as there was no significant decomposition observed when further treated to identical reaction conditions (up to 16 h). Thus, the presumed intramolecular rearrangement might be disfavored by either the addition of water as an intermolecular source of oxonium ion quench and/or by lowering the reaction temperature



Scheme 9. Proposed acid-catalyzed decomposition of **47**.

(i.e., room temperature). Indeed, using a 1:1 mixture of THF and 1 M HCl at room temperature provided the target compound.[60] However, the reaction was slow and typically halted at around 55% conversion after 72 h. Adding more acid, water or letting the reaction stir longer was not successful, and typically led to further decomposition. However, diluting the reaction from the outset greatly accelerated the deprotection, reducing the reaction to just 10 h (Scheme 10). As aldehyde **7** could not be isolated from unreacted **47** using standard techniques, the mixture was subjected directly to the intramolecular NHK coupling to provide neodolabellane **1**. Noteworthy, the NHK reaction provided the desired diastereoisomer, a consequence of the established strong conformational preference of the 11-membered macrocycle in neodolabellanes.[15b,61] IBX-mediated oxidation of the allylic alcohol (**1**) cleanly provided neodolabellane **2**. All spectral data were consistent with those reported for the nature-derived compounds.[12]



Scheme 10.

Conclusion

In summary, an assessment of synthetic strategies has been conducted for the preparation of neodolabellanes. Whereas the CM/RCM sequence (retrosynthesis A) proved unfruitful, the alternate Pd-catalyzed allylation and diastereoselective NHK coupling (retrosynthesis B) culminated in the preparation of neodolabellanes **1** and **2** in 8.8% (14 steps) and 8% (15 steps) overall yields, respectively. This report constitutes the first reported total syntheses of these compounds possessing this interesting molecular architecture.

Acknowledgement

We thank ORDCF and NSERC Canada for financial support and Dr. Howard Hunter, Dr. Debasis Mallik and Prof. Arturo Orellana for their valued collaborations.

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Received: June 13, 2008
Published online: July 30, 2008

