DOI: 10.1002/ange.200803284

Enantioselective Synthesis of the Carbocyclic D-Ring Subunit of Massadine**

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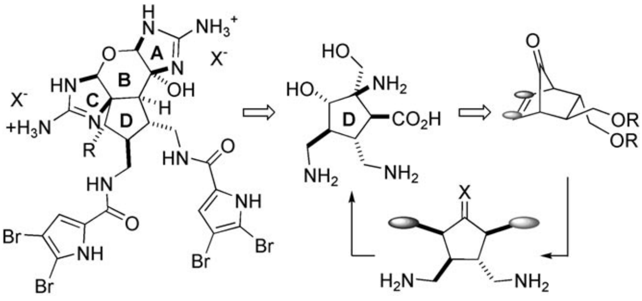
Pyrrole-imidazole marine alkaloids have attracted considerable attention as a consequence of their complex architecture and potent biological activity.[1] To date, more than 90 members have been identified,[1,2] including massadine (**1**) which was recently isolated from *Stylissa aff. Massa* (Figure 1).[3] The complexity associated with these densely functionalized, stereochemically rich alkaloids have made them veritable targets for synthesis studies. Herein we report an efficient asymmetric synthesis of the D-ring subunit embedded in massadine (**1**). Notable aspects of the strategy are: 1) the application of a cationic norbornyl rearrangement leading to facile functionalization, 2) an ozonolytic cleavage displaying remarkable end-group differentiation, and 3) a carboxy-inversion reaction for the installation of the requisite hindered secondary alcohol found in massadine (**1**). Collectively, these key transformations allow access to the fully functionalized carbocycle, which is a suitable launching point from which to address the challenges posed by the heterocycles in the natural product.

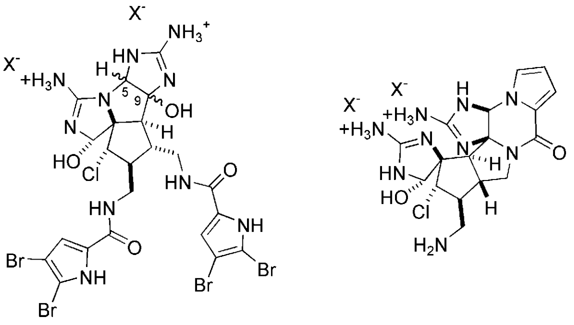


1 (R = OH): massadine
2 (R = Cl): massadine chloride

by single-step end-group differentiation

Figure 1. Retrosynthetic analysis for massadine (**1**).

The family of oroidin alkaloids, which includes axinellamines A (**3**) and B (**4**), palau'amine (**5**), and massadine (**1**), presents a collection of synthetic hurdles such as the asymmetric construction of a densely functionalized, stereochemically intricate core, and its implementation in a synthetic route to assemble the heterocyclic array. Axinellamines A (**3**) and B (**4**) have succumbed to total synthesis, albeit in racemic form.[4] Numerous efforts for the construction of the cyclopentane core, which is common to **2**–**5**, have been documented (Figure 1 and Figure 2).[5,6] However, massadine (**1**) presents a unique challenge because it possesses a hydroxy group instead of a chloro substituent (Figure 1). Thus, in contrast to the axinellamines, there have been no reports on the asymmetric total synthesis or on the formation of a fully functionalized and properly configured core fragment of **1** (Figure 1, R = OH on D ring).



3 (α-H5, α-OH9): axinellamine A
4 (β-H5, β-OH9): axinellamine B

5: palau'amine

Figure 2. Marine alkaloids axinellamine A (**3**) and B (**4**), and palau'amine (**5**).

In parallel to our earlier reports which focused on the synthesis of axinellamine, we decided to use a norbornene scaffold, albeit through the implementation of an altogether different strategy. The ensuing route described herein is considerably more efficient as the overall yield was improved by 19-fold.[6] The present synthesis commenced with the cycloaddition reaction of commercially available silane **6**[7] with di-(−)-menthyl fumarate in the presence of Et_2AlCl to give **7** in 92 % yield with a diastereoselectivity of greater than 95:5 (Scheme 1).[8]

Next, this adduct was treated with bromine, and following treatment with Ag^I, alcohol **9** was obtained in 96 % yield (two steps).[9] Although the mechanism for the conversion of **7** into **9** has not been studied in detail, a putative sequence of steps as postulated by Fleming et al. is presented in Scheme 2. We have found this reaction to be a highly reliable method for functionalization of the C7 position of norbornene, even on large scale (> 50 g).

When subjected to Swern oxidation conditions, alcohol **9** furnished the corresponding ketone, which was then masked

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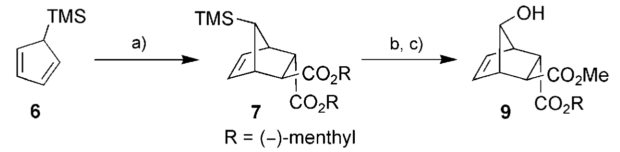
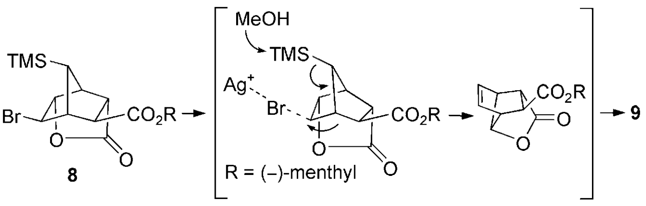
[**] This research was supported by Swiss National Science Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803284.

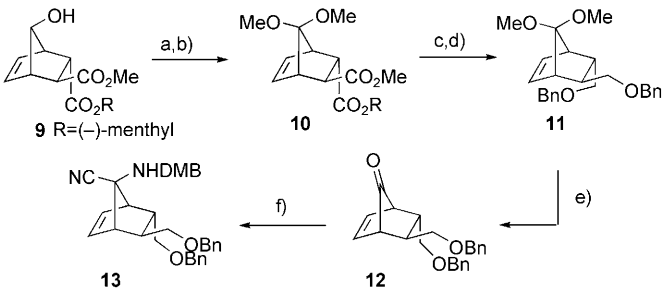


Scheme 1. a) (−)-Menthylfumarate, Et_2AlCl, toluene, −78 °C, 92%; b) Br_2, CH_2Cl_2, RT, 99%; c) $AgNO_3$, MeOH, 70 °C, 97%. TMS = trimethylsilyl.



Scheme 2.

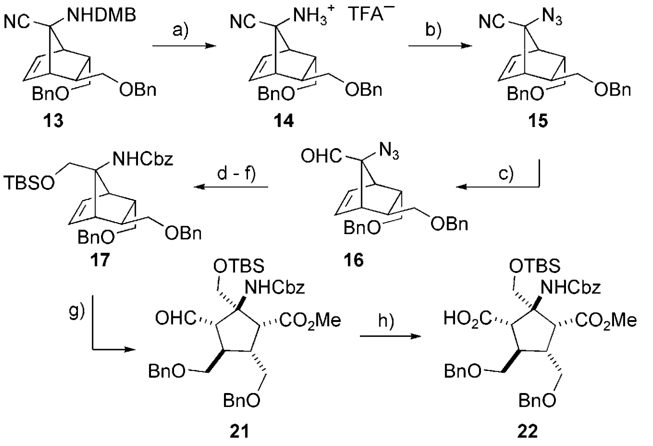
as the dimethyl ketal (**10**) in 92% yield (Scheme 3). Reduction of the esters in **10** with $LiAlH_4$ provided a diol that was subjected to benzylation, leading to **11** (90%).[10] Hydrolysis of the ketal gave access to norbornenone **12** (98%).



Scheme 3. a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, 89%; b) $HC(OMe)_3$, *p*-TsOH (cat.), MeOH, 50 °C, 92%; c) LAH, THF, 0 °C, 95%; d) KO*t*Bu, BnBr, dioxane, 90%; e) *p*-TsOH (15 mol%), THF/H_2O (4:1), reflux, 98%; f) $DMBNH_2$, *p*-TsOH (10 mol%), 4 Å M.S., toluene, 110 °C, then Me_3SiCN, $ZnCl_2$ (5 mol%), MeOH, RT, 95%; *p*-TsOH = *p*-toluenesulfonic acid; M.S. = molecular sieves; LAH = lithium aluminum hydride; Bn = benzyl; $DMBNH_2$ = 2,4-(MeO)-$C_6H_4CH_2NH_2$.

The stage was set for a Strecker aminocyanation reaction. In initial experiments involving ketone **12** reacting with Me_3SiCN and ammonia in the presence of Ti(O*i*Pr)$_4$, the corresponding cyanohydrin was the only product obtained. However, upon screening various amines, we found that benzylamines effectively participated in this transformation. Hence, the use 2,4-dimethoxybenzylamine led to aminonitrile **13** in 95% yield.[11] The aminocyanation proceeded with remarkable diastereoselectivity (> 95:5) as determined by ^{1}H NMR spectroscopic analysis. This selectivity most likely resulted from the efficient shielding of one of the iminium diastereofaces by the *exo*-positioned benzyloxymethylene substituent.[12]

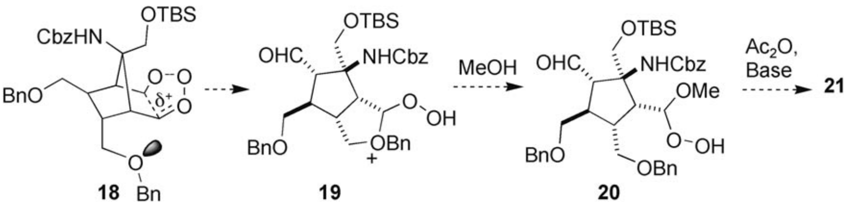
Nitrile reduction proved to be difficult with DIBAL-H at −78 °C and led to decomposition of the starting material. Compounds generated by exchange of the 2,4-dimethoxybenzyl group for all of the common amine protecting groups also met with extensive decomposition upon treatment with DIBAL-H. Confronted with these complications, we examined masking the amine as an azide. Although the use of azides as protected amines can be found in the carbohydrate literature, it is rather uncommon in natural products synthesis. The 2,4-dimethoxybenzyl group was removed by treatment of **13** with a mixture of trifluoroacetic acid, water, and triisopropylsilane, leading to **14** in 87% yield (Scheme 4). The azido group was then introduced through a copper(II)-catalyzed diazotransfer reaction involving the in situ formation of TfN_3 (79%).[13] Azidonitrile **15** proved compatible with the DIBAL-H reduction, furnishing desired aldehyde **16** in 92% yield.[14] Reduction of **16** to the corresponding alcohol and then protection with a TBS group proceeded in a 75% yield over three steps from **15**. Subsequently, the azido moiety was converted into a benzyl carbamate through a two-step procedure involving a Staudinger reduction and subsequent treatment with CbzCl to provide **17** in 93% yield.



Scheme 4. a) $CF_3CO_2H/H_2O/iPr_3SiH$, RT, 87%; b) NaN_3, Tf_2O, $CuSO_4{\cdot}5\,H_2O$, toluene/H_2O/MeOH (ca. 4:1:6), RT, 79%; c) DIBAL-H, toluene, −78 °C; d) $NaBH_4$, MeOH, 0 °C 77% (over 2 steps); e) TBSCl, imidazole, CH_2Cl_2, 98%; f) PMe_3, CH_2Cl_2/MeOH (2:1), RT, then CbzCl, $NaHCO_3$, acetone/H_2O (5:1), 93%; g) O_3, $NaHCO_3$, CH_2Cl_2/MeOH (5:1), −78 °C, then Ac_2O, NEt_3, CH_2Cl_2, 0 °C, 97%; h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, RT, 98%. Tf = trifluoromethanesulfonyl; DIBAL-H = diisobutylaluminum hydride; Cbz = benzyloxycarbonyl; TBS = *tert*-butyldimethylsilyl.

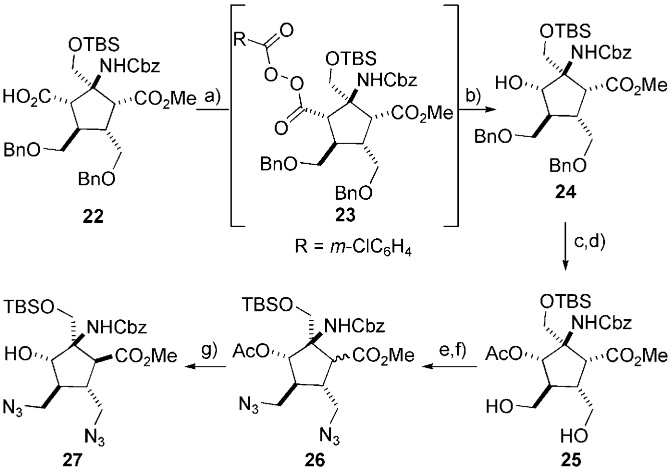
At this stage the synthetic route was at a strategically critical point, because cleavage of the norbornene to reveal a cyclopentane core would require conditions for distinguishing between the two sp^2-hybridized carbons. In this respect, we found particularly intriguing the possibility of effecting ozonolytic opening of **17** accompanied by regioselective end-group differentiation.[15,16]

When norbornene **17** was exposed to ozone in the presence of sodium bicarbonate, ester/aldehyde **21** was isolated as the only product in 97% yield. This transformation proved robust, even on a multigram scale. The structure and relative configuration of **21** were unambiguously established on the basis of NOE and two-dimensional NMR spectroscopic experiments. Although the precise mechanistic details for the selectivity in the ozonolysis remain unclear, we speculate that the presence of the proximal benzyloxy group is key to selective breakdown of primary ozonide **18**, possibly by the formation of hydroperoxide intermediate **19** (Scheme 5). The observed end-group differentiation is notable because it provides a tactical solution to the selective manipulation of the norbornene. Additionally, it is remarkable that the end-group differentiation occurs in the absence of strong inductive effects operating at the ends of the olefin.



Scheme 5.

The aldehyde in **21** was then oxidized to the corresponding acid (**22**) by using the protocol reported by Pinnick and co-workers.[17] Subsequent installation of the necessary hydroxy could be achieved with the standard Barton radical-decarboxylation method, albeit in unsatisfactory yield.[18] Consequently, we decided to explore the use of an alternative approach involving a carboxy-inversion reaction.[19] This was carried out by treating acid **22** with *m*CPBA in the presence of DCC. The resulting mixed diacyl peroxide was heated, and subsequent methanolysis provided **24** in 64% over two steps (Scheme 6). After acylation of **24**, the benzyl groups were selectively removed in the presence of the Cbz carbamate with BCl_3 to provide diol **25** in 67% over two steps. The mesylation of the diol followed by S_N2 displacement of the resulting mesyoxy groups with sodium azide afforded a diastereomeric mixture of diazides **26** and **27** (78%), which proved to be inconsequential. A screen of various conditions revealed Cs_2CO_3 to be ideal in effecting both saponification of the acetate as well as complete epimerization of the methyl ester to give desired **27** in 92% yield. The relative configuration of ester **27** was determined by NOE techniques.



Scheme 6. a) *m*CPBA, DCC, CH_2Cl_2, 0 °C, 87% (over 2 steps from **17**); b) toluene, 100 °C, then K_2CO_3, MeOH, 64%; c) Ac_2O, DMAP, pyridine, CH_2Cl_2, 94%; d) BCl_3, CH_2Cl_2, −78 °C, 71%; e) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C; f) NaN_3, 4 Å M.S., DMF, 60 °C, 78% (over 2 steps); g) Cs_2CO_3, MeOH, 92%. *m*CPBA = *meta*-chloroperbenzoic acid; DCC = dicyclohexylcarbodiimide.

In summary we have disclosed an enantioselective approach to the core fragment of massadine (**1**) which has 24 linear steps and an overall yield of 8.0% (average yield of ca. 90% per step) starting from commercially available silane **6**. The salient features of this route include: 1) the implementation of a stereospecific cationic norbornyl rearrangement to provide access to a highly functionalized intermediate in optically active form, 2) regioselective end-group differentiation through ozonolytic cleavage of an olefin, and 3) the use of a carboxy-inversion reaction for the installation of the key hindered hydroxy function found in the core. As an added benefit, acid **22** may be suitable for a decarboxylative chlorination which would permit a divergent route to access the core elements of structures **2**–**5**. The efficient synthesis sets the stage for the remaining daunting tasks en route to massadine (**1**), which involve the introduction of the heterocycles at the periphery of the carbocycle.

Received: July 7, 2008

Keywords: alkaloids · norbornenes · rearrangement · synthesis design

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