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Approach Towards an EPC-Synthesis of Nodusmicin - IV.[1]

Construction of the Highly Hindered Trisubstituted Double Bond of Nodusmicin.[2]

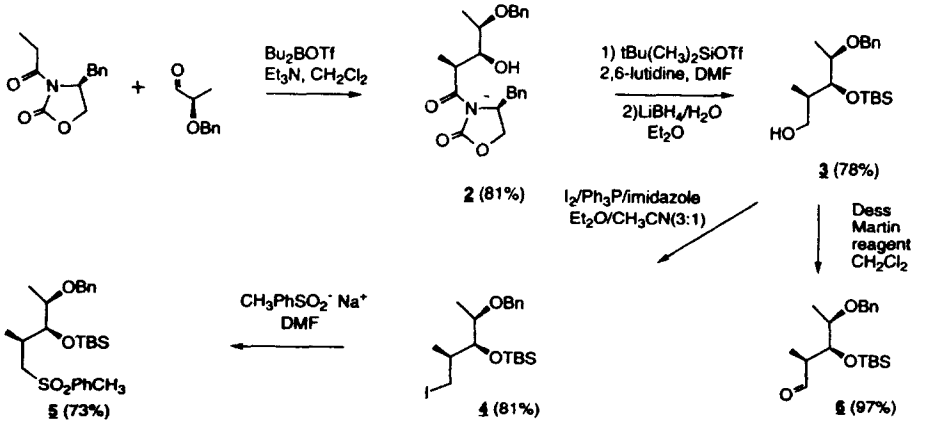
Edwin Auer, Edda Gössinger*, and Michael Graupe

Institut für Organische Chemie, Universität Wien, Währingerstr.38, A-1090 Wien

Abstract: The highly substituted subunit **6** of our convergent synthesis of nodusmicin was prepared utilizing Evans´ oxazolidinone protocol. Compound **6** was then adjoined to the decalin subunit **7** using Martin´s olefination method. To improve on the formation of the hindered trisubstituted double bond, the following model reactions were devised: reductive coupling of ester and keto functionality of tricycle **16** led to the α-hydroxyketone, which was converted to the cyclic sulfate **19** via the diol. Sodium naphthalide then converted **19** to the olefins **20**.

The increasing resistance of bacterial pathogens against antibiotics necessitates the development of new and effective antibiotic species.[3] We therefore chose nodusmicin **1**[4,5] due to its antibacterial activity and unusual structure as target of a convergent enantiomerically pure synthesis.

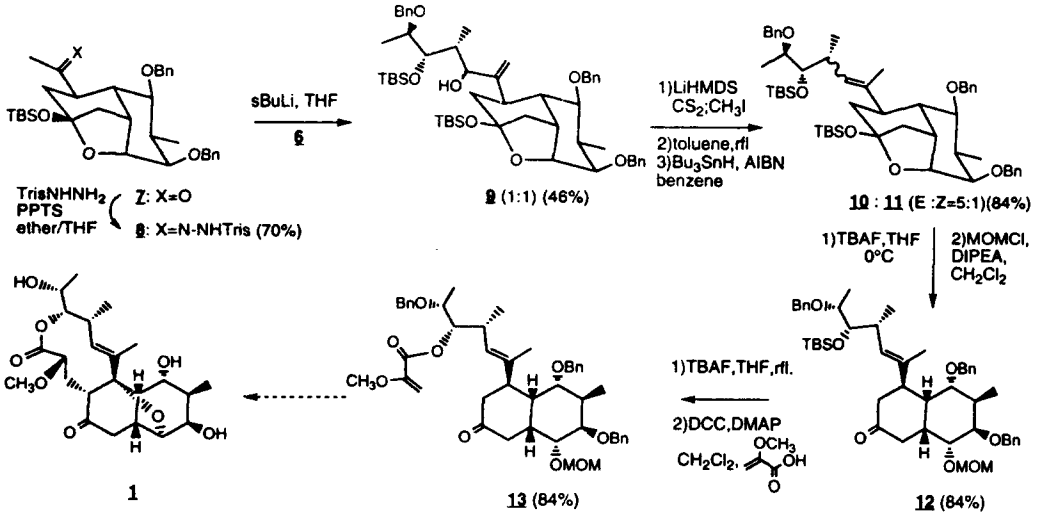
After completing the synthesis of the enantiomerically pure *cis*-decalin part of nodusmicin,[1] we prepared the second subunit, an enantiomerically pure, highly substituted, five-carbon chain using Evans´ enantioselective aldol protocol.[6] We report this synthesis and our efforts to connect the subunits with the formation of a highly congested trisubstituted double bond.



Scheme 1

The boron enolate of oxopropyloxazolidinone[6] was added to (R)-2-benzyloxypropanal[7] yielding the oxazolidinone derivative **2**.[2] X-ray analysis of the recrystallized compound **2** revealed that the expected stereoisomer was produced.[8] After transforming the alcohol **2** into its tert-butyldimethylsilyl-ether reduction by $LiBH_4$[9] afforded the primary alcohol **3**.

In a preliminary attempt, alcohol **3** was converted into the p-tolylsulfone derivative **5** via the iodide **4** according to Corey et al.[10] and consecutive treatment with sodium p-tolylsulfinate.[11] Several attempts to achieve the intended Julia reaction[12] with enantiomerically pure ketone **7**[1] failed due to severe steric hindrance at the carbonyl position. We then turned our attention to Martin's recently published olefination method[13] to prepare the desired trisubstituted double bond.

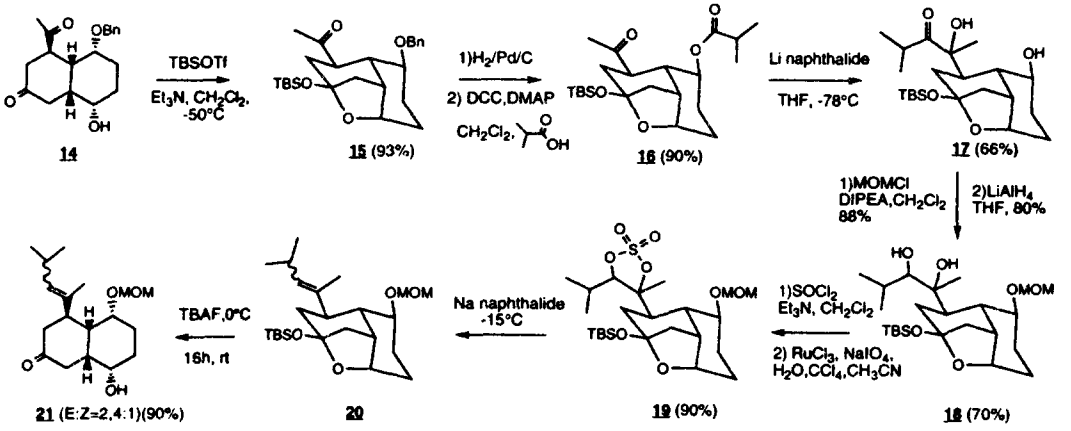


Scheme 2

Thus, enantiomerically pure **7** was converted to the vinyl lithium compound via the sulfonylhydrazone **8**[14] and reacted with aldehyde **6**, prepared by Dess-Martin oxidation[15] of alcohol **3**. A 1:1 mixture of allylalcohols **9** was obtained in 46% yield. This mixture was converted to the corresponding xanthates, and thermal [3,3]-sigmatropic rearrangement led to the dithiocarbonates in excellent yields. This rearrangement was highly stereoselective as each of the chromatographically separated xanthates led exclusively to a single dithiocarbonate. Subsequent desulfuration by tributylstannane afforded the olefins **10** : **11** as a 5 : 1 (E : Z) mixture regardless of the configuration of the double bond in the starting dithiocarbonate. The configuration of the double bond was deduced by NMR spectroscopy.[16] To connect the third and last subunit of our convergent synthesis, the olefins were transformed as follows. Partial desilylation with fluoride at 0°C cleaved the cyclic ketal. At this point, the two bicyclic olefins were separated by chromatography. The secondary alcohol of the purified E-olefin was protected as methoxymethyl ether **12**. Treatment with tetrabutylammonium fluoride at elevated temperature cleaved the exocyclic silyl ether, and the liberated alcohol was esterified with α-methoxy acrylic acid.[17] Thus all the subunits of our projected synthesis were adjoined.

Although we have succeeded in connecting the subunits in our projected synthesis, the modera-

te yields of the decisive coupling of the first two subunits tempted us to develop a new method to prepare the congested trisubstituted double bond by means of model compounds. Therefore, we chose 5-acetyl-7-benzyloxy-10-hydroxybicyclo[4.4.0]decan-3-one **14**[18] as the simplified model of the decalin moiety. As the smallest relevant open chained subunit the isobutyl group was elected.



Scheme 3

To diminish the free enthalpy of activation, we turned our attention to intramolecular carbonyl coupling reactions. Thus, diketone **14** was converted to the cyclic ketal **15** and debenzylated by hydrogenolysis. Esterification with isobutyric acid yielded **16**. Unfortunately, several attempts at the McMurry reaction[19] were tried to no avail. Therefore, we examined other variants of the pinacol type reaction.[20,21] By adjusting the reaction conditions to -78°C and 1,05 equivalents of lithium naphthalide,[22] the hydroxyketone **17** was obtained in good yields. After protection of the secondary alcohol of **17**, reduction with lithium aluminum hydride led to the vicinal diol **18**, which was converted to the cyclic sulfate **19** according to literature.[23] This cyclic sulfate was treated with sodium naphthalide affording a mixture of E- and Z-olefin **20** resp.(2,4 : 1) in high yield,[24] which was transformed to the bicyclic ketones **21**. We are now adjusting this method to the fully substituted subunits.

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21 a) With Li/NH_3 at -78°C, the keto group of **16** was reduced (40%) and only small amounts of the desired **18** (10%) were isolated. Compound **17** was not detected. b) Under acyloin reaction conditions (Na/K, TMSCl, ether, rt) intramolecular coupling of **16** proceeded in good yields but led, due to overreduction, to the silylenolether. c) With excess lithium naphthalide in THF at -78°C, **16** was converted via hydroxyketone **17** by deoxygenation to the corresponding ketone.

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