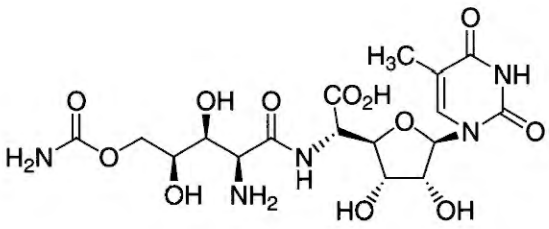
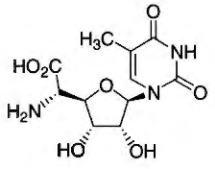


12

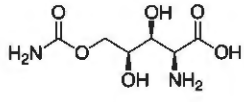
(+)-Polyoxin J (Gosh 1999)

12.1 Introduction

The polyoxins are an important group of peptidyl nucleosides isolated from the fermentation broth of *Streptomyces cacoi* var *asoensis* by *Isono* et al. in 1969.[1] About 15 compounds showing a closely related structure have been identified and designated with alphabetical letters. The characteristic skeleton of this class of antibiotics includes a peptide linkage between the nucleoside α-amino acid and polyhydroxynorvaline. As main difference among the polyoxins the nucleoside portion can bear different pyrimidine bases. For example polyoxin J is composed of thymine polyoxin C (**1**) and 5-*O*-carbamoyl polyoxamic acid (**2**). The polyoxins are attracting increasing interest as antifungal compounds since they exhibit potent activity against phytopathogenic fungi while being non-toxic to bacteria, plants, or animals.[2] These biological effects are closely related to the inhibition of the enzyme chitin synthetase and therefore the biosynthesis of chitin, an essential component of the fungal cell wall.[3] For example the polyoxins show high inhibitory potencies against isolated chitin synthetase from the human pathogen *Candida albicans*; however, against whole cells the polyoxins are inactive. Moreover, attention has been given to the polyoxins and the structurally related natural products nikkomycins[4] and neopolyoxins[5] because of their inhibitory effects on opportunistic fungal infection by *Candida albicans* in immunocompromised hosts, such as AIDS victims and organ transplant patients.[6]



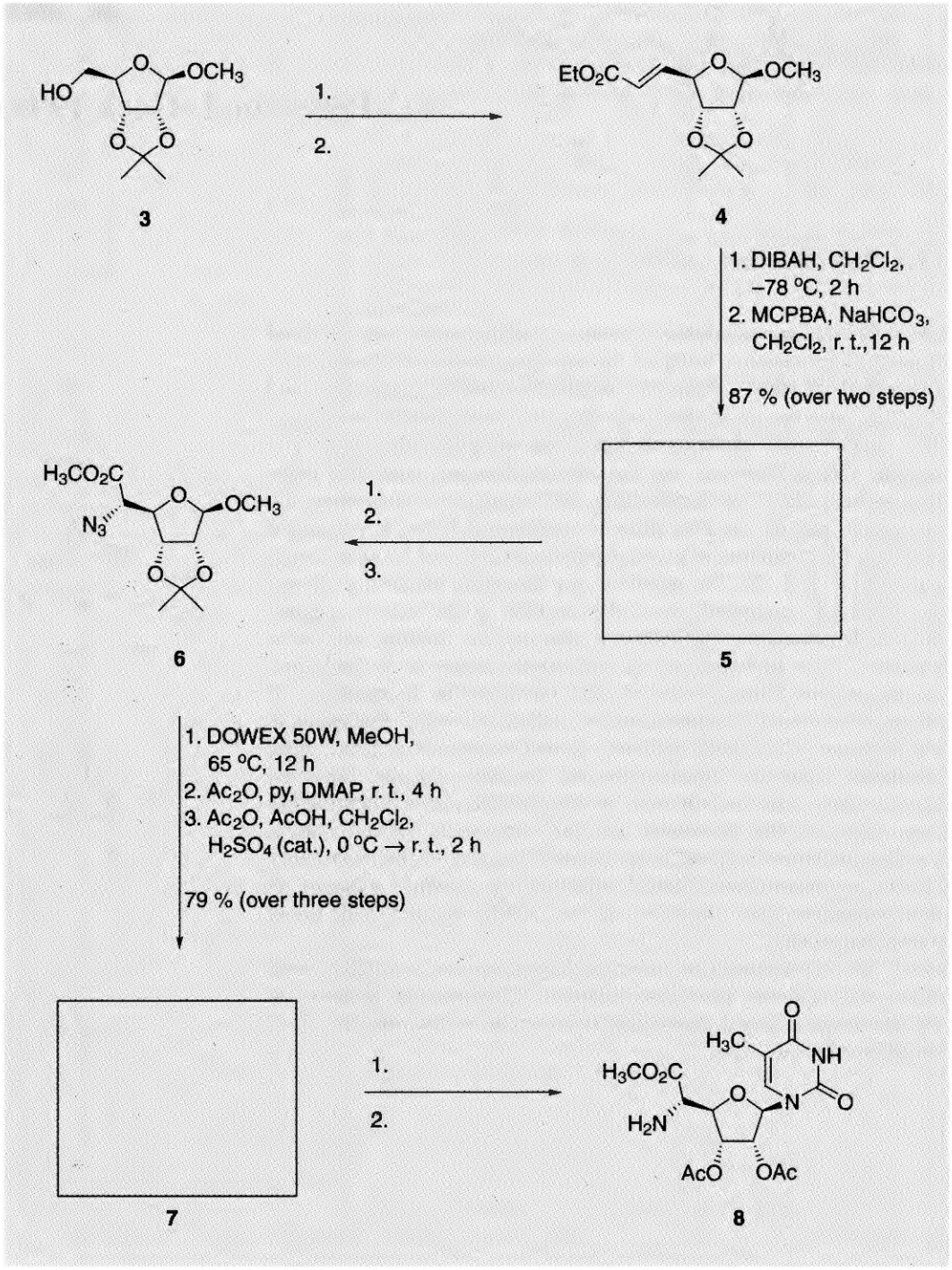
1

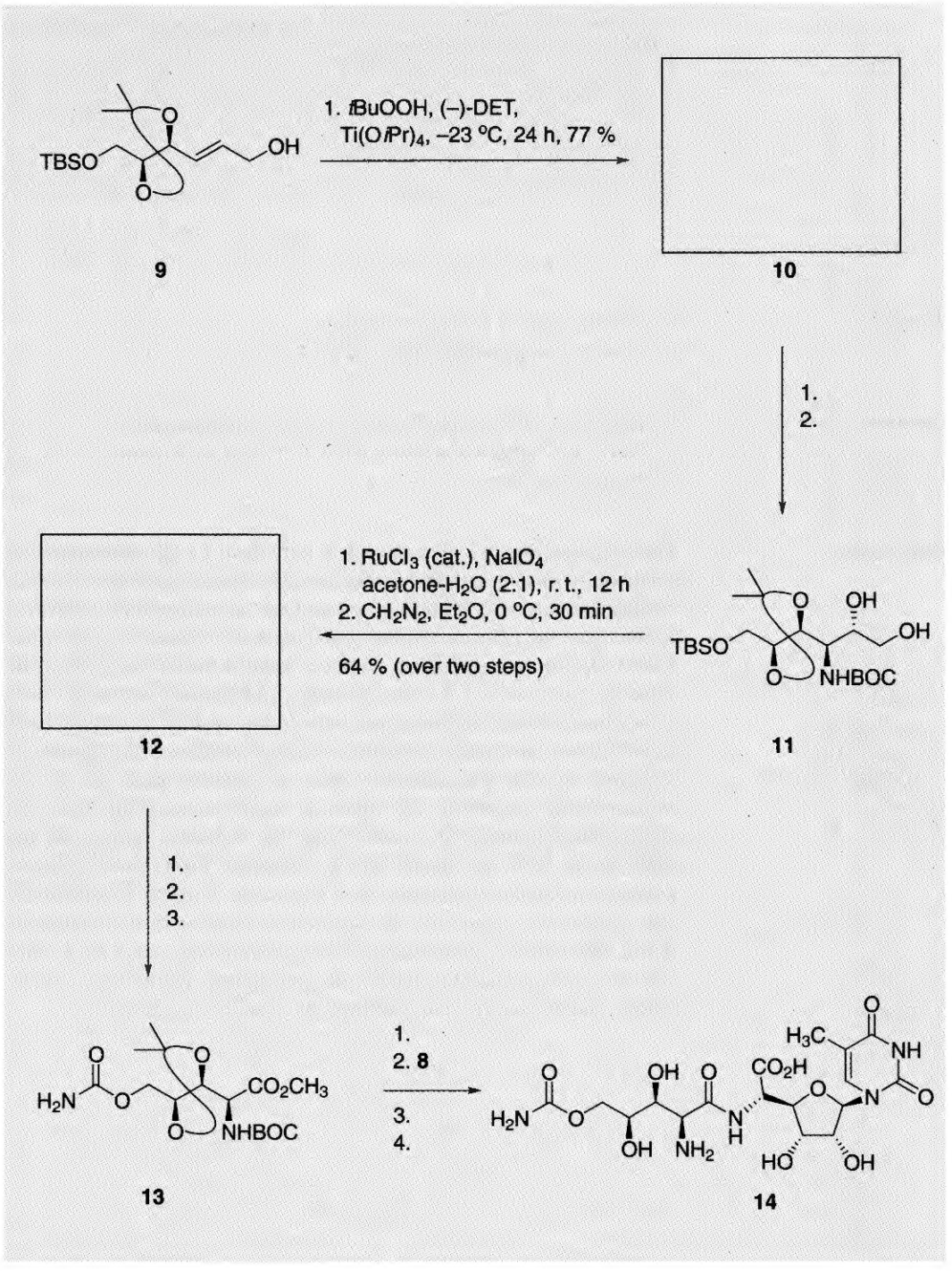


2

Since the first synthesis of polyoxin J by *Kuzuhara* in 1973 several other total syntheses have been reported.[7] This problem is based on the stereoselective and convergent total synthesis described by *Gosh* and co-workers in 1999.[8]

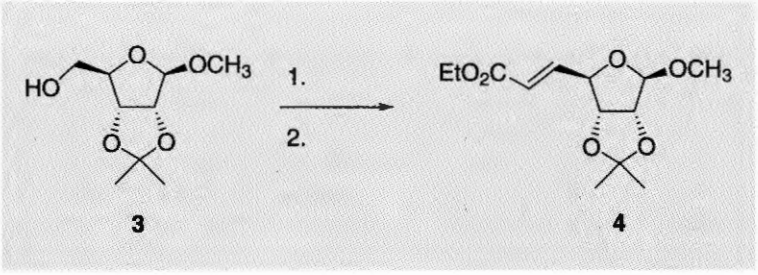
12.2 Overview




TBSO
OH
1. tBuOOH, (–)-DET,
Ti(OiPr)4, –23 °C, 24 h, 77 %
9
10
1.
2.
1. RuCl3 (cat.), NaIO4
acetone-H2O (2:1), r. t., 12 h
2. CH2N2, Et2O, 0 °C, 30 min
64 % (over two steps)
TBSO
OH
OH
NHBOC
12
11
1.
2.
3.
H2N
CO2CH3
NHBOC
1.
2. 8
3.
4.
H3C
NH
CO2H
OH
NH2
HO
13
14

12.3 Synthesis

Problem



3 4

Hints

- The first step is a *Swern* oxidation.
- Finally a phosphonoacetate is used.

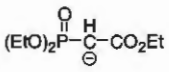
Solution

1. DMSO, $(COCl)_2$, CH_2Cl_2, –60 → 50 °C, 2 h then Et_3N
2. NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C → r. t., 30 min

72 % (over two steps)

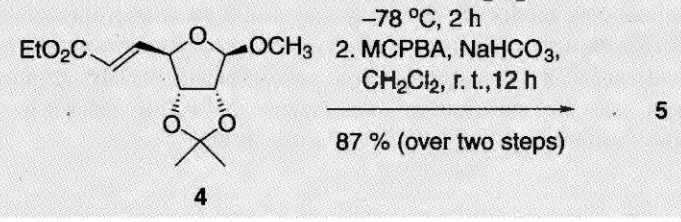
Discussion

The protected methyl glycoside **3** is converted to the corresponding aldehyde by *Swern* oxidation using oxalyl chloride activated DMSO. Further reaction with triethyl phosphonoacetate and sodium hydride – known as the *Horner-Wadsworth-Emmons* reaction – provides selectively the *trans* α,β-unsaturated ester **4** in 72 % yield. This valuable alternative to the *Wittig* olefination protocol uses phosphonate esters as substrates which are readily available from alkyl halides and trialkyl phosphites *via* the *Arbuzov* rearrangement.[9] Reaction of the phosphonate with a suitable base gives the corresponding carbanion **15** which is more nucleophilic than the related phosphorane. **15** reacts with the carbonyl group of the aldehyde to form an alkene and a phosphate ester. Such *Horner-Wadsworth-Emmons* reactions typically occur with *trans* selectivity (see Chapter 9). Generally, the reaction is superior to the analogous *Wittig* olefination. It gives better yields, phosphonate esters are readily available and furthermore the formed phosphate byproduct is water-soluble and thus easily removed from the reaction mixture.



15

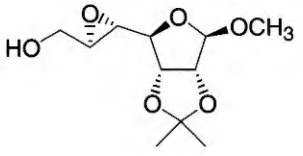
Problem



Hints

- DIBAH is a reducing agent.
- Which diastereofacial selectivity do you expect in step 2?

Solution

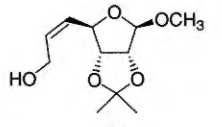


5

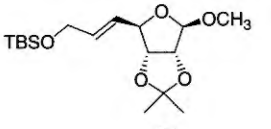
Discussion

DIBAH reduction of **4** at –78 °C provides the corresponding *trans*-allylic alcohol. Successive epoxidation with *meta*-chloroperbenzoic acid (MCPBA) yields a single *syn* epoxide **5**. The stereochemical assignment is proven by a second experiment using the asymmetric *Sharpless* epoxidation protocol. Both MCPBA and the *Sharpless* protocol using (–)-diethyl D-tartrate provided **5.**

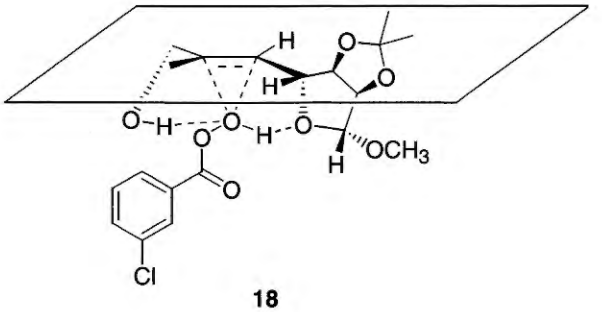
Interestingly, MCPBA epoxidation of *cis* alcohol **16** affords a mixture of diastereomeric epoxides (55:45 mixture). Furthermore, protection of the allylic alcohol as TBS ether (**17**) and subsequent epoxidation results as well in hardly any stereochemical selectivity (53:47 mixture). With regard to these results it is suggested that the *trans*-allylic hydroxy group is effectively involved in directing the MCPBA epoxidation event.



16



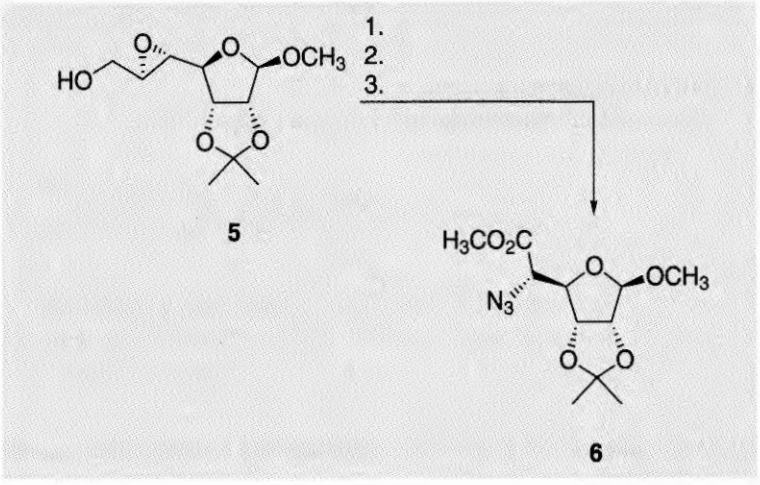
17



18

The diastereofacial selectivity is explained by the highly organized transition state model **18**. In this model, MCPBA is coordinated with the allylic hydroxy group as well as the ribofuranoside ring oxygen. The *cis* alcohol **16** cannot adopt such transition state geometry because of the developing nonbonded interaction between the ribofuranoside ring and the hydroxymethyl group.

Problem



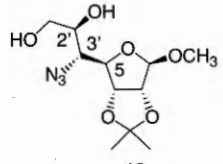
Hints

- The epoxide is opened by a titanium reagent.
- The resulting diol is cleaved.
- Step 3 generates an ester.

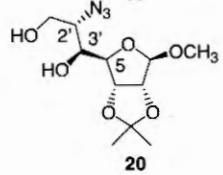
Solution

1. $Ti(OiPr)_2(N_3)_2$, benzene, 75 °C, 15 min, 79 %
2. $RuCl_3$ (cat.), H_5IO_6, MeCN/CCl_4/H_2O, r. t., 2 h
3. MeI, $KHCO_3$, DMF, r. t., 12 h, 80 % (over two steps)

Discussion



19



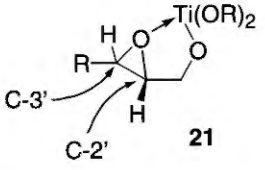
20

The azido group is introduced by a titanium-mediated nucleophilic opening of 2,3-epoxy alcohol **5** invented by *Sharpless*.[10] In principle, nucleophilic attack at C-2' or C-3' is possible.

Interestingly, treatment of **5** with diisopropoxytitanium diazide furnishes **19** and **20** as a nearly 4:1 mixture of regioisomers which are readily separated by silica gel chromatography. The major component of the mixture is azido diol **19** derived from C-3' attack.

Sharpless suggests that this regioselectivity originates from coordination of the epoxy alcohol to the metal center in a bidentate manner (**21**).[11] The bond between C-3' and oxygen appears much better orientated to overlap with an empty d-orbital on titanium than does the bond between C-2' and oxygen which lies nearly in the plane

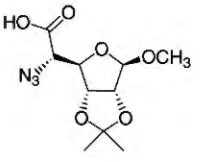
of the five-membered ring. In principle, the magnitude of the selectivity depends on steric and electronic factors. Thus, increasing steric hindrance at C-3' should result in decreased C-3' selectivity as well as the presence of electron-withdrawing groups at C-3'.



21

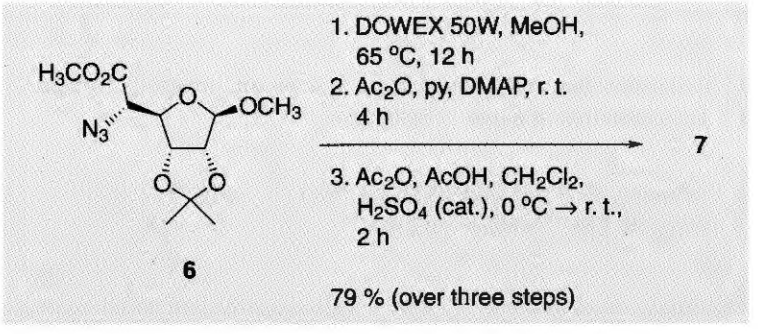
However, regiopure azido 1,2-diol **19** is converted to the corresponding azido carboxylic acid **22** by oxidative glycol cleavage with periodic acid in the presence of catalytic amounts of ruthenium trichloride. Interestingly, the use of sodium periodate instead of periodic acid resulted in a 10–15 % epimerization of the C-5 stereocenter.

The obtained acid **22** is treated with methyl iodide and potassium bicarbonate to afford azido methyl ester **6**.



22

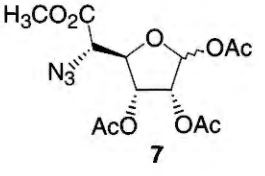
Problem



Hints

- DOWEX 50W is an acidic ion exchange resin.
- What is the difference between step 2 and 3?

Solution

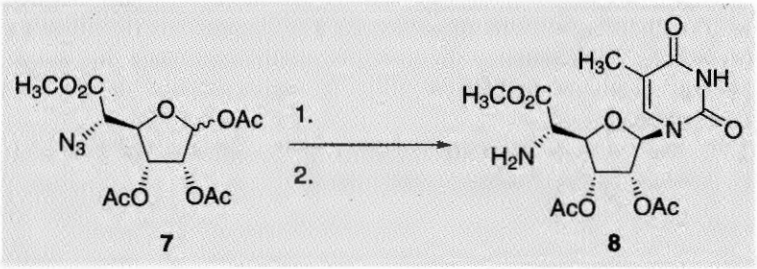


7

Discussion

In principle, acetals are cleaved by acid-catalyzed hydrolysis. In most cases aqueous acetic acid, aqueous trifluoracetic acid, dilute HCl in THF or DOWEX 50W (H^+) resin are used. Thus, treatment of **6** with DOWEX ion exchange resin in methanol rapidly furnishes the corresponding 1,2-diol without any further chromatographic purification steps. Generally, polymer supported reagents benefit from the ease of removal from the reaction mixture just by filtration of the insoluble resin. The resulting diol is acetylated by addition of acetic anhydride and pyridine. Final acetal exchange is achieved by acetic anhydride and catalytic amounts of concentrated sulfuric acid. A mixture (2:1) of anomers is obtained.

Problem



7 **8**

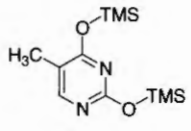
Hints

- In the first step an intermediacy 1,2-acyloxonium salt is formed.
- The azido functionality is reduced.

Solution

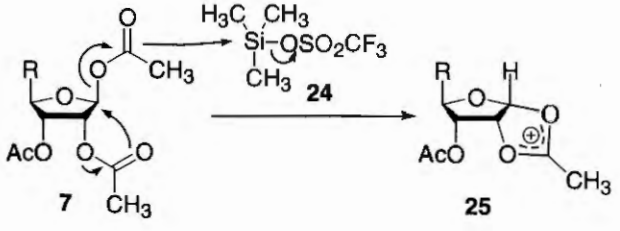
1. Thymine-bis-TMS, TMSOTf, $Cl(CH_2)_2Cl$, 84 °C, 1 h, 91 %
2. H_2, 10 % Pd/C, MeOH, 2 h, 98 %

Discussion

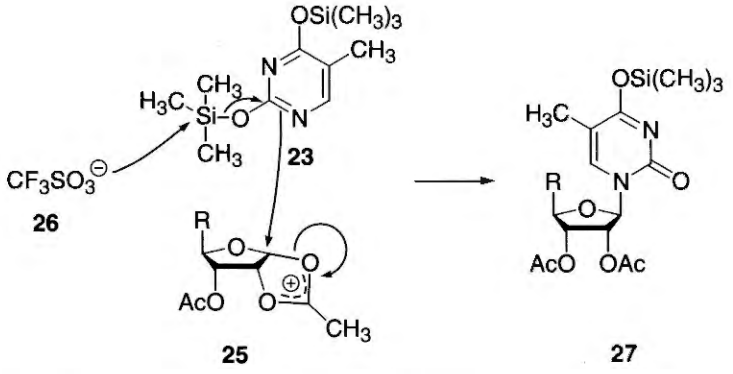


23

Exposure of triacetate **7** to 5-methyl-2,4-bis(trimethylsilyloxy)-pyrimidine (**23**) in presence of TMSOTf (**24**) provides the protected β-nucleoside **8**. The reaction of silylated heterocyclic bases with peracylated carbohydrates in the presence of *Friedel-Crafts* catalysts yields selectively β-nucleosides.

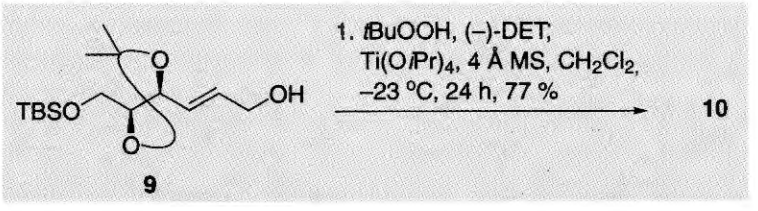


The mechanism is explained *via* the formation of the rather stable 1,2-acyloxonium salt **25** (neighbor group effect).
The activated α-trimethylsilyl group on the pyrimidine moiety reacts with the triflate ion **26** to regenerate the triflate catalyst. Under reversible and thus thermodynamically controlled conditions, the nucleophilic silylated base **23** attacks the carbohydrate cation **25** only from the top (β-side) to afford exclusively the β-nucleoside.



Further hydrolysis yields the protected β-nucleoside **27**.
The azido functionality is finally hydrogenated by means of hydrogen in presence of catalytic amounts of palladium on activated charcoal to furnish **8**.

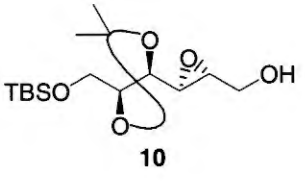
Problem



Hints

- The reaction is known as *Sharpless* epoxidation.
- Which stereochemistry do you expect?

Solution

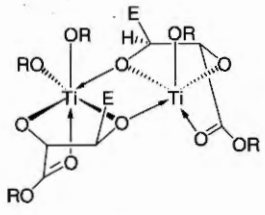


Discussion

The known allylic alcohol **9** derived from protected dimethyl tartrate is exposed to *Sharpless* asymmetric epoxidation conditions with (–)-diethyl D-tartrate. The reaction yields exclusively the *anti* epoxide **10** in 77 % yield. In contrast to the above mentioned epoxidation of the ribose derived allylic alcohol, in this case epoxidation of **9** with MCPBA at 0 °C resulted in a 65:35 mixture of *syn/anti* diastereomers.

The *Sharpless* epoxidation of primary and secondary allylic alcohols discovered in 1980 is a powerful reagent-controlled reaction.[12] The use of titanium(IV) tetraisopropoxide as catalyst, *tert*-butylhydroperoxide as oxidant, and an enantiopure dialkyl tartrate as chiral auxiliary accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity. If the reaction is kept absolutely dry, catalytic amounts of the dialkyl tartrate(titanium)(IV) complex are sufficient.

Sharpless and his co-workers studied the mechanism of the oxidation and established the following characteristics: Participation of the free hydroxy group of the substrate is evidently essential for the selectivity. Enantioselectivity is at its optimum at 1:1 rates of $Ti(OiPr)_4$ and tartrate ester. Mixing of the reagents results in formation of a dimeric species. This species was initially believed to be a ten-membered ring, however, because of IR, NMR as well as X-ray studies on the closely related complex titanium (dibenzyltartramide)$_2$(OR)$_4$; structure **28** was suggested to represent the reagent in the absence of substrate and oxidant.[13] Kinetic experiments on the addition of the substrate and the oxidant have shown that the remaining two isopropyloxy ligands are displaced by allyloxy and *tert*-butylhydroperoxy groups as shown in **29**. The reactants are preorganized on the metal in a chiral environment prior to the reaction yielding the corresponding epoxide **30**.



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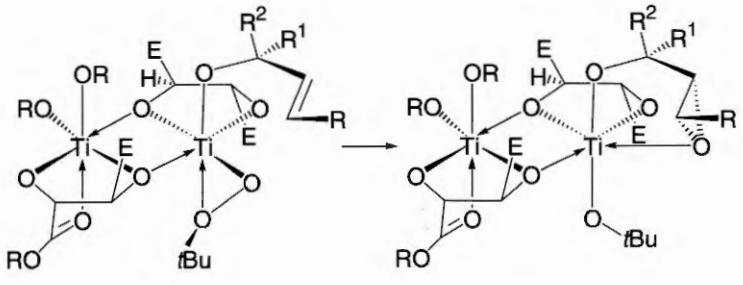
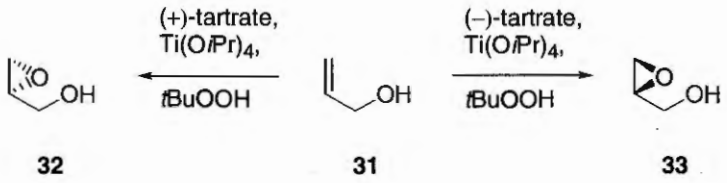


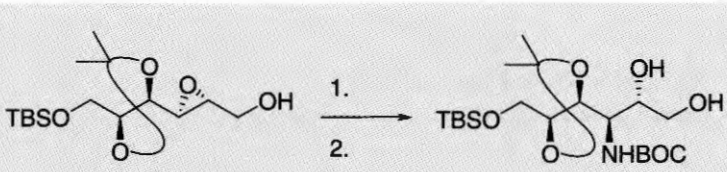
29 **30**

Thus, the reaction is very predictable. When a (–)-tartrate ligand such as (–)-DET (diethyl tartrate) or (–)-DIPT (diisopropyl tartrate) is used, the oxygen atom is delivered to the top face of the olefin when the allylic alcohol is depicted as in **31**. The (+)-tartrate ligand, on the other hand, allows the bottom face to be epoxidized.



32 **31** **33**

Problem



10 **11**

Hints

- The first step has already been mentioned in this chapter.
- Step 2 is a combined reduction/protection operation.

Solution

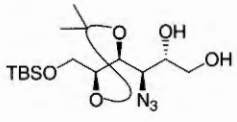
1. $Ti(OiPr)_2(N_3)_2$, PhH, 72 °C, 15 min, 96 %, 3:1 mixture
2. H_2, 10 % Pd/C, BOC_2O, EtOAc, 12 h

60 % (over two steps)

Discussion

The azido group is again introduced by a titanium mediated reaction. The regioselective ring opening of **10** with diisopropoxy-titaniumdiazide in benzene at 72 °C affords the azido diols **34** and **35** as an inseparable 3:1 mixture.

However, the catalytic reduction of the azido functionalities in the presence of BOC_2O yields the corresponding BOC-protected hydroxy amine which is easily separated by silica gel chromatography. The variation of the conditions did not improve the mixture ratio of the azido diols. However, **11** could be isolated in 60 % yield in that two step sequence.



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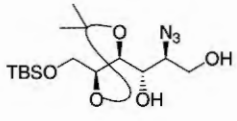

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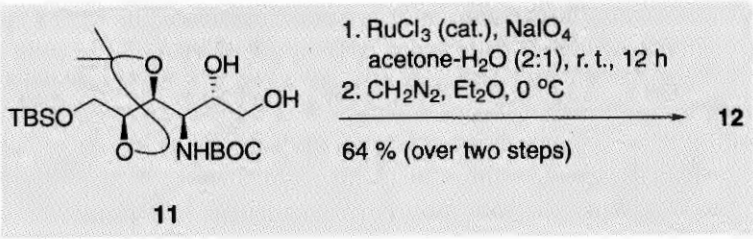
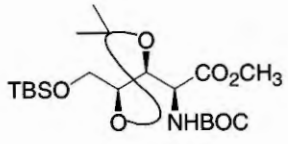
Problem



Hints

- The diol is cleaved and oxidized.
- Step 2 generates an ester.

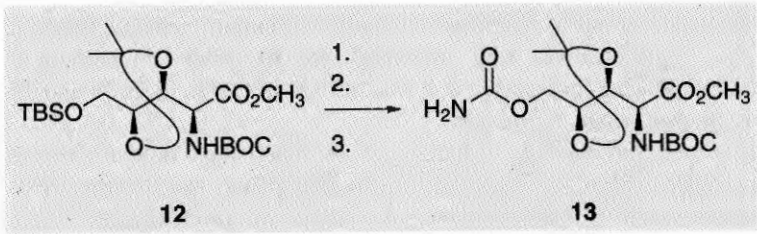
Solution



Discussion

Again the diol is oxidized to the carboxylic acid with RuO_4 generated from $RuCl_3$ and $NaIO_4$. Subsequent esterification with diazomethane (see Chapter 13) yields **12** in 64 % over two steps.

Problem



Hints

- A protecting group is removed.
- The urethane is formed *via* a carbonate.

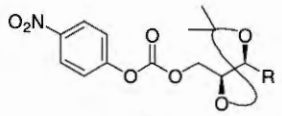
Solution

1. AcOH-THF-H_2O (3:1:1), r. t., 12 h
2. *p*-NO_2Ph-OCOCl, pyridine, 0 °C, 1 h
3. NH_4OH, THF, 0 °C, 30 min

85 % (over three steps)

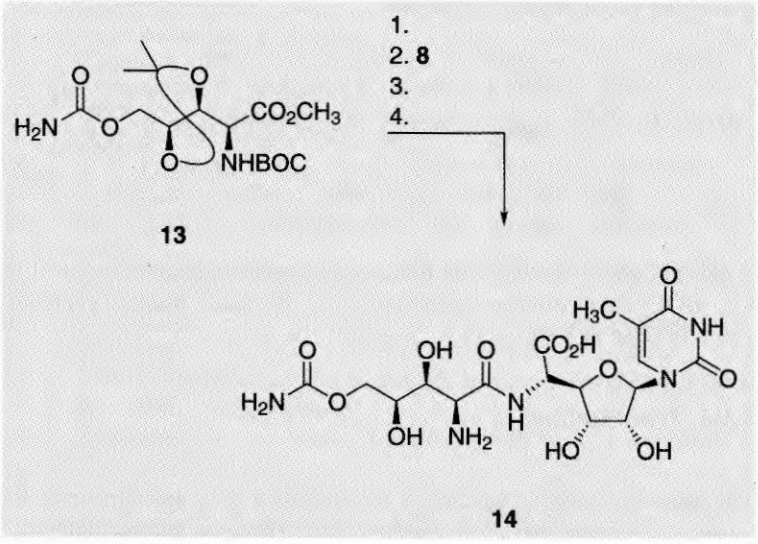
Discussion

The TBS-group is removed selectively by treatment of **12** with aqueous acetic acid at room temperature for 12 h.
The carbamoylation of **12** was carried out in a one-pot procedure under standard conditions, i. e. treatment with *para*-nitrophenyl chloroformate followed by ammonolysis of the resulting carbonate **36** to give the urethane in 85 % over three steps.



36

Problem



Hints

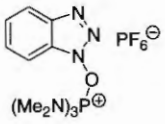
- Saponification of the ester is followed by coupling with **8** using a peptide coupling reagent.
- What peptide coupling reagents do you know?
- Two more deprotections are necessary.

Solution

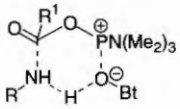
1. $LiOH{\cdot}H_2O$, $THF\text{-}H_2O$ (1:5), 0 °C, 2 h, 90 %
2. **8**, BOP, $i Pr_2NEt$, DMF, r. t., 12 h, 63 %
3. $LiOH{\cdot}H_2O$, $THF\text{-}H_2O$ (1:5), 0 °C, 2 h
4. CF_3CO_2H, 0 °C, 2 h, 53 % (over two steps)

Discussion

The synthesis of (+)-polyoxin J **14** is completed by selective ester hydrolysis with aqueous lithium hydroxide. The resulting carbamoylpolyoxamic acid was then coupled with the protected thymine polyoxin C **8** with the BOP reagent (*Castro's* reagent)[14] (benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluoro-phosphate) **37** to furnish the peptide derivative in 63 % yield.

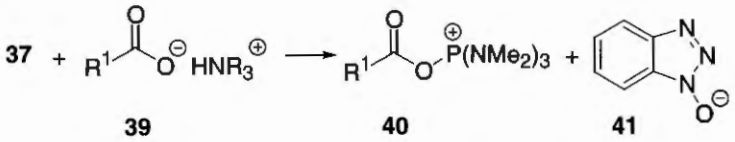


37



38

The BOP reagent **37** was first prepared to act as a coupling agent (dehydrating agent phosphonium salt) as well as a racemization suppressor (benzotriazole additive). Early investigations have indicated a benzotriazolyl active ester as reactive intermediate like in the activation with the DCC/HOBT reagent system. Now it is believed that the acyloxyphosphonium salt **40** is formed directly presumably through the cyclic complex **38**.[15] No reaction occurs until a tertiary base, *N*-methylmorpholine, triethylamine, or diisopropylethylamine, is added to form salt **39**. Under such conditions the coupling rate is so high that racemization is neglected.



39 **40** **41**

Deprotection of the acid with lithium hydroxide and acidic removal of the BOC and isopropylidene groups afforded finally synthetic polyoxin J **14** in 53 % yield.

12.4 Conclusion

The stereoselective synthesis of (+)-polyoxin J is accomplished by *Gosh* in 24 steps and 3 % overall yield. The key intermediates are protected thymine polyoxin C **8** and the 5-*O*-carbamoyl polyoxamic acid **2**, which were synthesized from D-ribose and dimethyl L-tartrate. Key steps are two different epoxidation reactions, one carried out with MCPBA and the other under *Sharpless* conditions with the D-(–)-tartrate. Both epoxides are opened with diisopropoxytitanium diazide. The coupling of the two fragments was realized with the BOP reagent **37**. This synthesis provides an easy access to the synthesis of various (+)-polyoxin J analogs for biological evaluation.

12.5 References

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