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Stereoselective and Efficient Synthesis of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol

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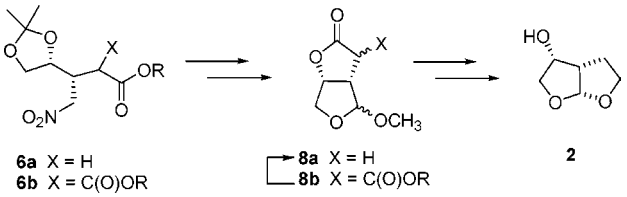
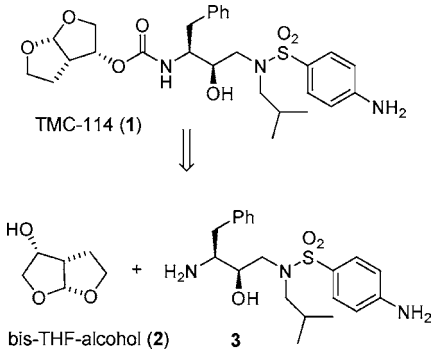
ABSTRACT



Two short and efficient synthesis routes have been developed for bis-THF-alcohol 2, a key building block of the investigational HIV protease inhibitor TMC114 (1). Using *S*-2,3-*O*-isopropylideneglyceraldehyde (4) as the source of chirality, both routes are based on a diastereoselective Michael addition of nitromethane to give predominantly the *syn* congeners 6 followed by a Nef oxidation and cyclization to afford lactone acetals 8, which are reduced and cyclized to give 2.

Inhibition of the proteolytic HIV protease enzyme has proven to be an effective treatment against AIDS, especially in combination with the use of reverse transcriptase inhibitors.[1] However, most current HIV protease inhibitors (PIs) contain peptide-like fragments bearing the usual disadvantages of peptide-based drugs. For that reason, and also because drug resistance has emerged against the existing peptidic PIs, focus in anti-AIDS research has recently been put on the development of nonpeptidal congeners active against PI-resistant mutants. Hence, Ghosh et al. developed a set of nonpeptidyl HIV PIs incorporating novel high-affinity P2-ligands and (*R*)-(hydroxyethylamino)sulfonamide isosteres.[2] Of particular interest is the PI TMC114 (**1**) which is being developed by Tibotec and is currently undergoing phase III clinical trials.[3] The molecule possesses a bis-tetrahydrofuranyl ("bis-THF")



moiety as the P2 ligand, of which the significance in withstanding in vitro drug resistance compared to the 3(*S*)-THF ligand is now well-recognized.[4] The bis-THF moiety is introduced into TMC114 by alkoxycarbonylation[5,6] of

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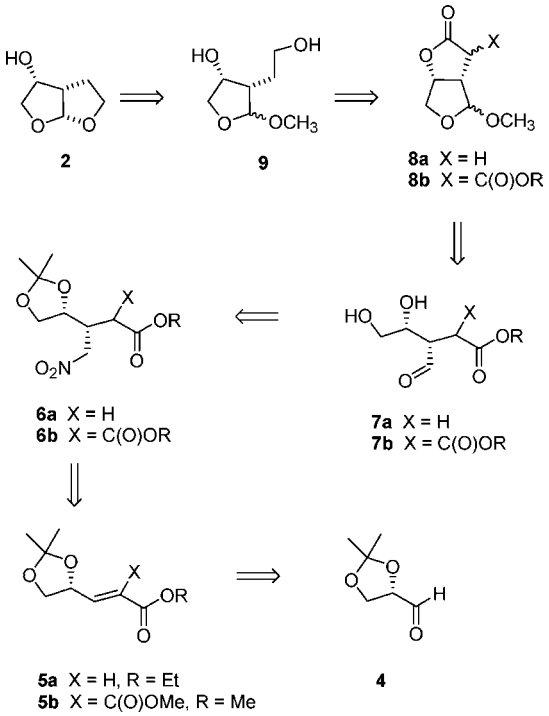
Scheme 1. Synthetic Strategy (R = Alkyl)



amine **3** with an activated mixed carbonate of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol **2**. For the synthesis of compound **2**, two approaches have been developed by Ghosh et al. A first approach,[5] based on radical cyclization combined with an ozonolytic alkene cleavage, is cost-inefficient and not amenable to scale-up. Moreover, the enzymatic resolution of the resulting racemic **2** gives the desired enantiomer of **2** in only 95% ee. A second recently reported approach[6] is based on a photochemical conjugate addition of 1,3-dioxolane to a protected 5(*S*)-hydroxymethyl-2(5*H*)-furanone derivative. Apart from the fact that photochemical reactions are usually difficult to scale-up, the latter building block also requires a multistep synthesis from expensive starting compounds and is obtained in only 92% ee. In addition, although the photochemical addition is almost completely diastereoselective, it furnishes the wrong *exo*-**2** diastereomer which requires epimerization to the desired *endo*-**2** congener using expensive and environmentally unfriendly oxidation/reduction chemistry. To support the clinical trials of TMC114, multi-100 kg quantities of **2** were required in >99% ee. Therefore, a stereoselective, efficient, and upscalable process was desired. In this paper, we report the development of two novel closely related routes to **2**, both satisfying these conditions.

We embarked on the strategy as shown in Scheme 1. The central compound in this route, lactone acetal **8a**, was to be reduced to diol **9** giving, upon acid-mediated cyclization, the desired *endo*-**2** diastereomer. The stereochemistry at the 4-methoxy position in **8a** seemed of no importance since cyclization of diol **9** was expected to occur in a *syn*-selective fashion. Lactone acetal **8a** was the expected result of the lactonization and acetal cyclization of diol aldehyde **7a** which was to be formed through a Nef reaction and simultaneous acetal deprotection of nitro compound **6a**. The key step in the synthetic pathway was a highly diastereoselective Michael addition of nitromethane to a protected γ,δ-dihydroxy-substituted α,β-unsaturated ester **5a**, the latter being accessible by a Wittig reaction on *S*-2,3-*O*-isopropylideneglyceraldehyde **4**[7] which is relatively inexpensive and available on industrial scale through a three-step process from L-ascorbic acid.[8] A diastereoselective Michael addition seemed crucial, since the formation of undesired *anti*-isomer of **6a** would contaminate the desired (endo) alcohol **2** with its exo congener.

Patrocinio et al.[9] reported that the Michael addition of nitromethane to **5a** (R = Me or Et) was slow and gave only moderate yields (70%) of the nitro adduct **6a** (R = Me or Et) with a *syn*/*anti* ratio of up to approximately 9:1. In our hands, we obtained a maximum *syn*/*anti* ratio of 85:15 (as determined by ^{1}H NMR), despite examining various bases and optimizing the reaction conditions. We anticipated that the use of a diester **5b** instead of monoesters **5a** would not only significantly speed up the Michael addition with nitromethane due to electronic reasons but also render this conjugate addition significantly more diastereoselective[10] due to steric effects. Diester **5b** was thought to be easily accessible by a Knoevenagel reaction of aldehyde **4** with dimethyl malonate.

Hence, we first examined this dimethyl malonate based route which would include the decarboxylation of the lactone acetal **8b** to **8a** prior to the reduction step to give diol **9**. The results of this examination are summarized in Scheme 2. The Knoevenagel reaction of aldehyde **4** with dimethyl malonate in THF proceeded well in the presence of pyridine (optimally 0.5 equiv) or a base with a similar pK_a value and using an excess (optimally 3 equiv) of acetic anhydride to promote the dehydration step. Use of a strong base without a dehydrating agent predominantly yielded byproducts. The maximal isolated yield of diester **5b** was 77% due to side reactions consisting of acid-catalyzed isopropylidene acetal shifts. The subsequent Michael addition of nitromethane to **5b** ran smoothly at ambient temperature in the presence of 0.1 equiv of DBU in methanol. Gratifyingly, the diastereoselectivity was high with a *syn*/*anti* ratio of 97:3 (as

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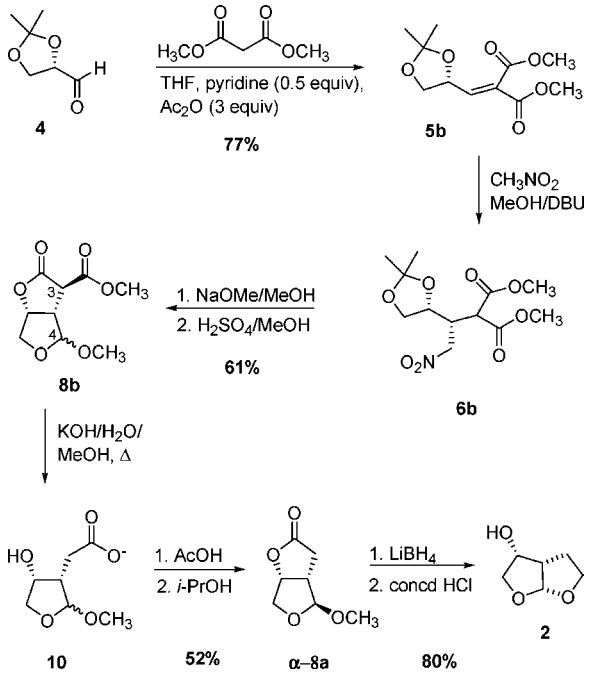
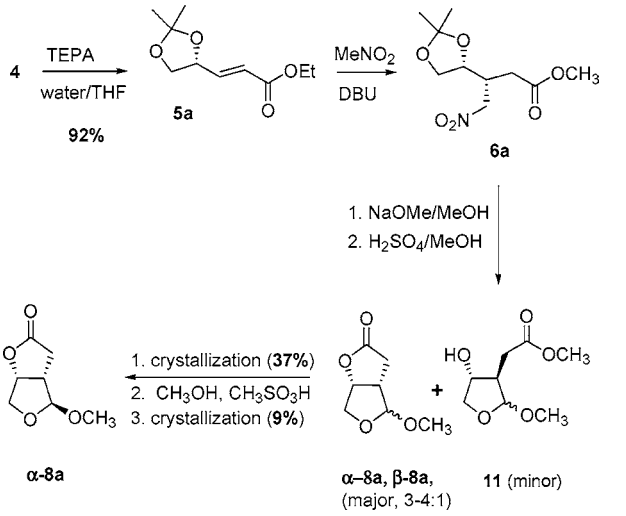
Scheme 2. Dimethyl Malonate Based Route



Scheme 3. "Wittig Route"



determined by ^{1}H NMR). The crude reaction mixture containing **6b** was then subjected to one equiv of NaOMe in MeOH and the resulting deprotonated nitro compound was slowly added to a concentrated solution of excess H_2SO_4 in methanol at 0−5 °C. Indeed, the lactone acetal **8b** turned out to be the major product of the reaction cascade, as a mixture of the four diastereomeric forms of which the two 3*R*-diastereomers prevailed. The α/*β*-anomeric ratio (i.e., the ratio of the (3*R*,4*S*)- vs the (3*R*,4*R*)-diastereoisomer) was 3−4:1 and could be enhanced to 6:1 by keeping the temperature during the acid quench <−5 °C. Although **8b** could be isolated by aqueous workup and extraction in 61% yield (based on diester **5b**), it appeared thermal and base labile. Decarboxylation of **8b** with concomitant lactone hydrolysis was accomplished by refluxing with 1.5 equiv of KOH in MeOH/water. Cyclization of the resulting hydroxy acid **10** in acetic acid was clean but slow and required over 12 h at 30 °C for completion. Attempts to accelerate this reaction by using stronger acids (such as formic acid) or higher reaction temperatures failed due to elimination of water and/or methanol from the tetrahydrofuran moiety of **8a** and **10**. After aqueous workup and crystallization from 2-propanol, α-anomeric lactone acetal α-**8a** was obtained in 52% yield based on **8b** in high chemical and diastereomeric purity. With α-**8a** in hand, reduction to the corresponding diol **9** proceeded smoothly with $LiBH_4$ in THF at 50 °C. The product was difficult to isolate since breakdown of its lithium complex with acid induced immediate cyclization to bis-THF-alcohol **2**. Direct cyclization was feasible by treatment of the lithium complex with a small excess (based on $LiBH_4$) of aqueous 32 wt % HCl. To avoid acid-catalyzed elimination of methanol and water from the tetrahydrofuran ring it was crucial to add the HCl solution over several hours and keep the temperature of the reaction <−5 °C. Isolation of **2** by aqueous workup proved difficult due to its high water solubility. However, **2** could be isolated in high chemical and diastereomeric (de > 99%) purity by neutralizing the acidic cyclization mixture with triethylamine and performing a solvent-switch to ethyl acetate. Filtration of the scarcely soluble salts and evaporation provided **2** in 80% yield (based on α-**8a**).

Although this six-step route, having an overall yield of 19%, was a significant improvement compared to the literature procedures and proved robust and reliable in the production of multi-100 kg quantities, we recognized some clear disadvantages. First, the Knoevenagel reaction had a maximal yield of 77%. Second, the decarboxylation and (re)-cyclization steps, apart from long reaction time and large reactor volume, involved extensive product loss (almost 50%) due to the polymerization reactions and difficulties with product isolation. Third, due to the lability of lactone ester **8b**, the aqueous workup conditions were sensitive to temperature and pH and required large reactor volumes.

These drawbacks and our observation that pure lactone acetal **8a** could be obtained from a dark-brown mixture of several components by one crystallization from 2-propanol prompted us to reconsider a "Wittig route" based on monoester **5a.** These results are summarized in Scheme 3.

Aldehyde **4** could be converted to enoate **5a** by a Horner−Wadsworth−Emmons variant of the Wittig reaction with 1 equiv of triethyl phosphonoacetate (TEPA) at pH = 10−11 in aqueous THF. Enoate **5a** could be obtained in high chemical and enantiomeric purity (ee = 98%) with an *E*/*Z* ratio of >95:5 in yields of up to 90% based on **4**. Of practical value was the fact that aldehyde **4,** obtained directly from the periodate oxidation of 5,6-*O*-isopropylidene-L-gulono-1,4-lactone in aqueous solution,[8] could be used. This water tolerant route offered a significant advantage over the dimethyl malonate based process where the Knoevenagel reaction demanded anhydrous aldehyde **1,** therefore requiring laborious extraction and coevaporation procedures. Subsequent Michael addition of nitromethane to enoate **5a** required

an examination of a wide range of bases, such as alkali alkoxides and hydroxides, tetra-*n*-butylammonium fluoride (TBAF), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,1,3,3-tetramethylguanidine (TMG). In all cases, the *syn*/*anti* ratio of the resulting nitro adduct **6a** was approximately 85:15 and the maximal conversion of **5a** (*E* + *Z*) to **6a** (*syn* + *anti*) was 80%. Subjection of **6a** to various amounts of NaOMe in MeOH and subsequently exposing the mixture into excess H_2SO_4 in methanol at 0−5 °C afforded lactone acetal **8a.** Use of alkali alkoxides, hydroxides or TBAF as a base in the Michael addition provided an overall crude yield of **8a** based on **5a** of 40% with an α/*β*-ratio (i.e., the ratio of the 4*S*- and 4*R*-diastereoisomers, α-**8a** and *β*-**8a**, respectively) of only 2.5−3.3:1. Surprisingly, the use of DBU and TMG in the Michael addition resulted in increased crude yields (50−56%) and α/*β*-ratios (3.2−3.8:1) of lactone acetal **8a**. Apparently, the counterion to the nitronate anion plays a pivotal role in the efficiency of the Nef reaction. Optimally, 1.1 equiv of NaOMe was used to deprotonate **6a** and the alkaline solution added to 3.5 equiv of 50 wt % H_2SO_4 in methanol at 0−5 °C over 3 h followed by aqueous workup (excess $KHCO_3$, final pH = 4.0) and extraction with ethyl acetate. This furnished **8a** in up to 56% yield based on alkene **5a** with an α/*β*-ratio of approximately 3.8:1. Interestingly, the majority of *anti*-isomers **11**, which due to steric contraints were in the noncyclized form, remained in the aqueous phase. Despite the high *β*-**8a** content in the crude **8a,** crystallization from 2-propanol furnished the α-anomerically pure lactone acetal α-**8a** in 37% yield based on alkene **5a**. Additionally, it was feasible to epimerize *β*-**8a** in the mother liquor (α/*β* ratio < 1:1) to mainly α-**8a** using 0.2 equiv of methanesulfonic acid in methanol (final α/*β* ratio 3:1). Subsequent neutralization with triethylamine and crystallization from 2-propanol gave a second crop of α-**8a** corresponding to an additional 9% yield. Both crops displayed an ee of >99% and a higher chemical purity than the crystalline α-**8a** as obtained previously and could be converted to bis-THF alcohol **2** in high (80%) yield. Hence, the Wittig route proved to be superior based on the overall yield of **2** (34% vs 19%), the reduced number of synthetic operations (4 vs 6), reactor volume efficiencies and ease of operation. The Wittig process has been run successfully on multi-100 kg scale but additional optimizations are being explored. The results of these improvements will be published in full in due course.

In conclusion, we have developed two routes toward **2** based on aldehyde **4**. Although both routes are highly diastereoselective and upscalable, the Wittig route has proven to be superior.

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Supporting Information Available: Experimental procedures, spectroscopic, ee, and purity data of **2**, **5a**, **5b**, α-**8a**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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