Tetrahedron Letters 49 (2008) 6980–6983

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The first asymmetric synthesis of all four isomers of *cis*- and *trans*-3,4-dihydroxy-3,4-dihydromollugin

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ARTICLE INFO

Article history:
Received 6 August 2008
Accepted 17 September 2008
Available online 27 September 2008

ABSTRACT

Asymmetric synthesis of all the four stereoisomers of *cis*-3,4-dihydroxy-3,4-dihydromollugins **4** and **6** and *trans*-3,4-dihydroxy-3,4-dihydromollugins **5** and **7** was achieved. The *O*-methoxymethyl mollugin derivatives were dihydroxylated to (−)- and (+)-*cis*-3,4-dihydroxy-3,4-dihydromollugin derivatives using both AD-mix-α and AD-mix-β. Deprotection of the MOM-ethers of *cis*-dihydroxy compounds resulted in the targeted stereoisomers (−)-(3*R*,4*R*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **4**, (−)-(3*R*,4*S*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **5**, (+)-(3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **6** and (+)-(3*S*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **7**. These routes were paved with difficulties, for example, incompatibility of the substrates with AD-mixes, the unexpected formation of *trans*-dihydroxy compounds and failures in deprotection protocols.

1. Introduction

Mollugin **1** and its analogues *cis*-3,4-dihydroxy-3,4-dihydromollugin **2** and *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** have been isolated from *Pentas longiflora* and *Rubia cordifolia*, and constitute a class of benzisochromene natural products with potent biological activities.[1] The Sharpless asymmetric dihydroxylation using preformed AD mixes is an excellent and practical method to prepare dihydroxy compounds with high enantioselectivity.[2] However, poor enantioselectivities were obtained in the case of *cis*-olefins with an exception of *cis*-allylic and homoallylic alcohols.[3,4] Only limited reports are found in the literature for the asymmetric dihydroxylation of cyclic *cis*-disubstituted olefins, such as chromenes, using AD-mixes. To the best of our knowledge, the highest obtained ee's for chromenes were only up to 70% using commercially available AD-mixes.[5]

Very recently, we reported the racemic syntheses of dihydroxymollugins **2** and **3**.[6] The *cis*-dihydroxy compound **2** was synthesized by a dihydroxylation reaction using OsO_4, and the *trans*-dihydroxy compound **3** was prepared using oxone on *O*-protected mollugin derivatives. The synthesis of racemic *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** has been reported by Wang et al, by reacting dimethyldioxirane (DMD) with mollugin **1** in 62% yield.[7] In our hands, by employing the same reaction conditions the *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** was only formed in 30% yield along with the formation of several side products. The selective asymmetric synthesis of all the four stereoisomers **4**–**7** has not been reported yet. In continuation of our work herein, we wish to report the first enantioselective synthesis of all four stereoisomers of 3,4-dihydroxy-3,4-dihydromollugin **4**–**7**.

2. Results and discussion

At the beginning, the synthesis of both stereoisomers of (−)-(3*R*,4*R*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **4** and (+)-(3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **6** was attempted. The strategy for the synthesis of target compounds was based on Sharpless asymmetric dihydroxylation reaction using AD mixes. As encountered in the previous case, due to complex formation of the osmium species with the acidic phenolic hydroxyl moiety of mollugin **1**, only complex reaction mixtures were obtained by attempted dihydroxylation of mollugin **1** using AD-mix-α and AD-mix-β.[6] Therefore, reactions were attempted on the protected mollugins such as the *O*-methyl ether protected mollugin **8** using AD-mix-β in a solvent mixture of *t*-BuOH:H_2O (1:1). After stirring for 24 h at 0–10 °C, the corresponding dihydroxy compound **9** was formed in 10% yield along with several unidentified side products (Scheme 1). Repeated endeavours by changing the solvent mixture (*t*-BuOH:H_2O, 1:1.5 or 1.5:1) failed. On the other hand, the addition of a small amount of tetrahydrofuran (THF) resulted in the improvement of the yield of dihydroxy compound (+)-(3*S*,4*S*)-**9**. Thus, the reaction of methyl ether protected mollugin **8** with AD-mix-β in a solvent mixture of *t*-BuOH:H_2O:THF (8:8:1) at 0–10 °C for 24 h afforded the methyl ether of (+)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **9** in 33% yield, along with the corresponding α-hydroxyketone **10** in 20% yield (Scheme 1), and together with unidentified products. Having this result in hand,

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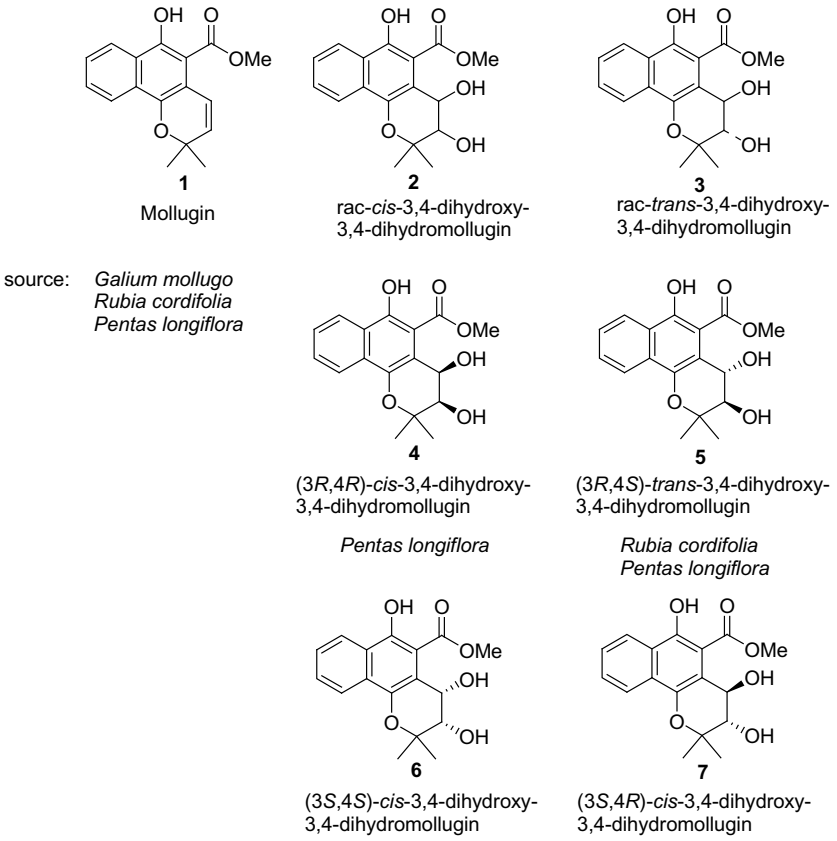
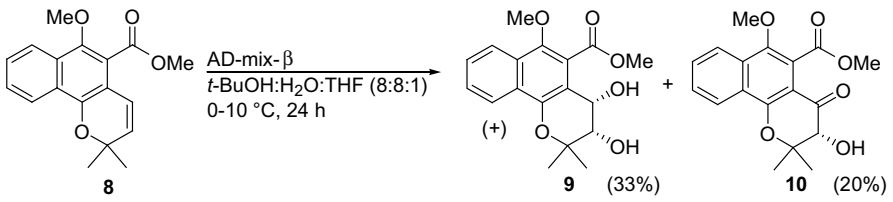
doi:10.1016/j.tetlet.2008.09.138



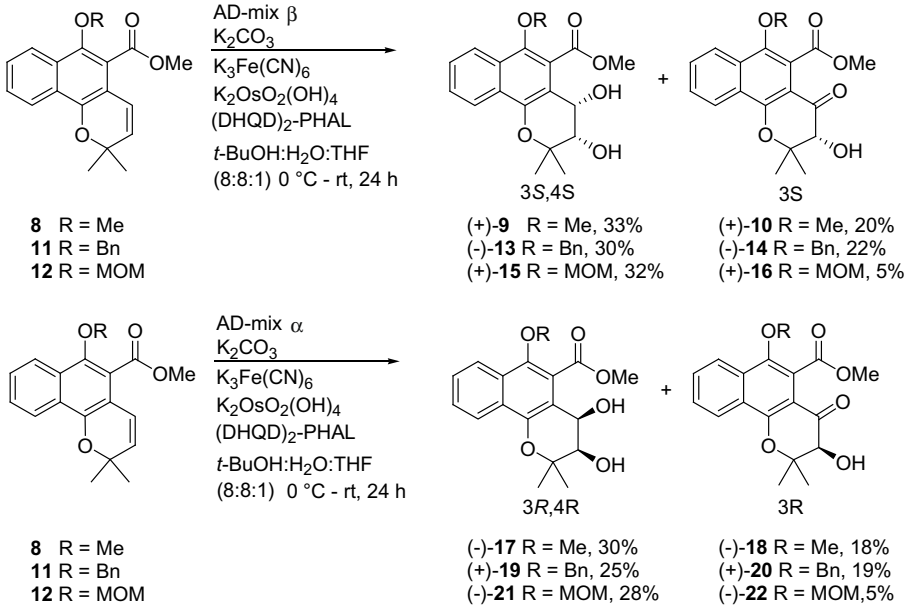
the effect of methanesulfonamide as an additive and the amount of AD-mixes were explored in order to improve the yield.

In general, the standard AD procedure calls for 1.4 g of AD-mix per millimole of olefin and 1 equiv of $MeSO_2NH_2$ for all substrates other than terminal alkenes.[2b] Surprisingly, the addition of $MeSO_2NH_2$ diminished the yield. Thus, a reaction was carried on *O*-methyl mollugin **8** using AD-mix-β in the presence of 1 equivalent of $MeSO_2NH_2$ in a solvent mixture of *t*-BuOH:H_2O:THF (8:8:1) at 0–10 °C for 48 h affording only 18% of the (+)-(3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydro mollugin **9**, along with several unidentified side products. It was also observed that, either increasing or decreasing the amount of AD-mix leads to complex reaction mixtures with diminished yields of the dihydroxy compound **9**. In order to investigate the effect of the protecting group to further improve the yield of the dihydroxy compound, the phenolic hydroxy moiety of mollugin was protected with different protecting groups.

Thus, mollugin **1** was protected as the *O*-benzyl and *O*-methoxymethyl ether[6] and subsequently asymmetric dihydroxylation reactions were attempted on these *O*-protected mollugins (Scheme 2). No significant improvement in the yield of the required dihydroxy compound was observed both with the *O*-benzylmollugin **11** and mollugin methoxymethyl ether **12**. The *O*-benzyl compound **11** provided the corresponding *cis*-diol **13** in 30% yield (hydroxyketone **14**, 22%), whereas the methoxymethyl ether of mollugin **12** gave the corresponding *cis*-dihydroxy compound **15** in 32% yield, along with only a small amount of the hydroxyketone **16** (5%). The yields were not changed much by switching AD-mix-β to AD-mix-α. The yields of dihydroxy compounds as well as hydroxy ketones were a little higher (30–33% for diols, 5–22% for hydroxyketones) with AD-mix-β, when compared to AD-mix-α 25–30% for diols, 5–19% for hydroxy ketones). The absolute configuration of dihydroxy compounds **9**, **13** and **15** that are formed with AD-mix-β were assigned as 3*S*,4*S* using the enantioselective mnemonic of the AD reactions and by comparing analogous dihydroxylations in the literature.[8] Similarly, the dihydroxy compounds **17**, **19** and **21** which were formed with AD-mix-α, were assigned as 3*R*,4*R*. The enantiomeric excess of the compound (+)-(3*S*,4*S*)-**15** was determined by ^{1}H NMR experiments of the corresponding compound with Pirkle alcohol as a chiral co-solvent.[9] Thus, the highest enantioselectivity was obtained in the case of *O*-methoxymethyl-(3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **15** using AD-mix-β[10] and was found to be 84% ($[\alpha]_D^{25}$ +10.9, *c* 1.3, $CHCl_3$) (see Table 1). Using AD-mix-α, 78% ee was found in the case of *O*-methoxymethyl-(3*R*,4*R*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **21** ($[\alpha]_D^{25}$ −11.0, *c* 1.75, $CHCl_3$).



Scheme 1.

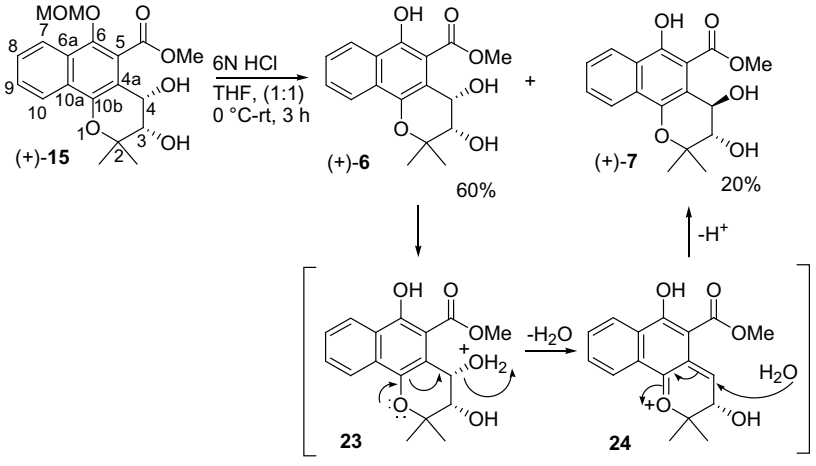


Scheme 2.

Table 1
Optical rotations of 3,4-dihydroxy-3,4-dihydromollugin derivatives (**9**,**13**,**15**,**17**,**19**,**21**) and the corresponding hydroxy ketone compounds (**10**,**14**,**16**,**18**,**20**,**22**)

Entry	Compound	Optical rotation (in $CHCl_3$)
1	**9**	$[\alpha]_D^{25}$ +4.2, *c* 1.00
2	**10**	$[\alpha]_D^{25}$ +4.4, *c* 2.10
3	**13**	$[\alpha]_D^{25}$ −10.8, *c* 1.00
4	**14**	$[\alpha]_D^{25}$ −1.1, *c* 2.10
5	**15**	$[\alpha]_D^{25}$ +10.9, *c* 1.30
6	**16**	$[\alpha]_D^{25}$ +1.5, *c* 2.50
7	**17**	$[\alpha]_D^{25}$ −3.4, *c* 0.55
8	**18**	$[\alpha]_D^{25}$ −3.1, *c* 0.75
9	**19**	$[\alpha]_D^{25}$ +9.6, *c* 0.25
10	**20**	$[\alpha]_D^{25}$ +3.0, *c* 0.50
11	**21**	$[\alpha]_D^{25}$ −11.0, *c* 1.75
12	**22**	$[\alpha]_D^{25}$ −1.8, *c* 3.00
13	**4**	$[\alpha]_D^{25}$ −9.6, *c* 0.75
14	**5**	$[\alpha]_D^{25}$ −11.2, *c* 0.75
15	**6**	$[\alpha]_D^{25}$ +10.7, *c* 1.25
16	**7**	$[\alpha]_D^{25}$ +12.5, *c* 0.75

Subsequently, having *O*-protected *cis*-3,4-dihydroxy-3,4-dihydromollugins in hand, research was focused on the deprotection of these compounds to obtain the targeted optically active 3,4-dihydroxy-3,4-dihydromollugins **4** and **6**. However, the deprotection reactions attempted on *O*-methyl dihydroxy compounds **9** or **17** either using boron(III) bromide in CH_2Cl_2 or using ceric(IV) ammonium nitrate in CH_3CN led to the formation of complex reaction mixtures. Similarly, the *O*-benzyl deprotection of dihydroxy compounds **13** or **19** using 10 mol % of Pd(0) in different solvents under H_2 atmosphere or using 2.5 equiv of CAN in CH_3CN failed. As explained in a previous article, racemic *O*-methoxymethyl 3,4-dihydroxy-3,4-dihydromollugin was successfully deprotected using 6 N HCl in THF.[6] Similarly, the deprotection reaction of *O*-methoxymethyl-(3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **12** carried out using 18 equiv of 6 N HCl in THF at 0 °C for 3 h, resulted in the formation of the required (3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **6** in 60% yield along with the corresponding *trans* isomer (3*S*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **7** in 20% yield. The ee of compound **4** was found to be 83% by comparing the optical rotation of the natural product {$[\alpha]_D^{25}$ +10.7, *c* 1.2,



Scheme 3.

$CHCl_3$; lit $[\alpha]_D^{25}$ −12.9, *c* 0.35, $CHCl_3$)}[1h,11]. This unusual formation of a *trans*-diol **7** from *cis*-diol **6** can be explained as follows (Scheme 3). Deprotection of the MOM-ether (+)-**15** obviously results in (+)-*cis*-diol **6**. However, under excess acidic conditions the hydroxyl moiety at position 4 is protonated and easily eliminated by an electron push mechanism starting from the electron lone pair of the pyranyl-oxygen. In this way, a reactive charged ortho-quinomethide intermediate **24** is formed to which water attacks and results in the formation of the more stable *trans* isomer (+)-**7**.

3. Conclusion

The asymmetric syntheses of (−)-(3*R*,4*R*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **4**, (−)-(3*R*,4*S*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **5**, (+)-(3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **6** and (+)-(3*S*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **7** was achieved for the first time. Although the lower yields and side products are the drawbacks of this protocol, the enantioselectivities are good to excellent. These reactions showed that much experimentation was necessary to achieve the dihydroxylation of such pyranes due to side reaction at all stages of the synthetic protocol.

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10. The general experimental procedure for AD of *O*-protected mollugin derivatives **8**–**12** using AD-mixes by taking compound **12** with AD-mix-β as a representative example. To a stirred solution of AD-mix-β (1.4 g) in *t*-BuOH:H_2O (1:1 v/v, 8 ml) was added a THF solution (0.5 ml) of compound **12** (328 mg, 1 mmol) at 0 °C. After stirring the resulting solution at 0–10 °C for 24 h, a saturated solution of aqueous sodium bisulfite (10 ml) was added, stirred for 1 h and then extracted with dichloromethane (3 × 20 ml). The combined organic layers were washed with brine (20 ml), dried over magnesium sulfate, and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 60/40 R_f 0.8) affording (+)-(3*S*,4*S*)-methyl *cis*-3,4-dihydroxy-6-methoxymethoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo-[*h*]-chromene-5-carboxylate **15** in 32% yield and (+)-(3*S*)-methyl 3-hydroxy-6-methoxymethoxy-2,2-dimethyl-4-oxo-3,4-dihydro-2*H*-benzo[*h*]-chromene-5-carboxylate **16** in 5% yield (petroleum ether/ethyl acetate 80/20 R_f 0.6).
11. The experiments carried out with Pirkle alcohol as a chiral resolving agent were not much useful in determing the enantiomeric excess of the compounds at this stage.