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Efficient Synthesis of (+)-MK7607 and its C-1 Epimer via the Stereoselective Transposition of a Tertiary Allylic Alcohol

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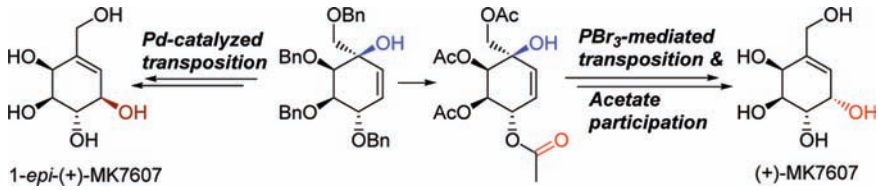
ABSTRACT



These studies provide an efficient and stereoselective synthetic route to (+)-MK7607 and its C-1 epimer from a common intermediate in high overall yields. The synthetic methodologies mainly rely on the stereospecific 1,3-allylic transposition of the hindered tertiary alcohol group through a palladium-catalyzed allylic rearrangement as well as a PBr_3-mediated allylic-transposed bromination.

(+)-MK7607 (**1**, Figure 1) is an unsaturated carbapyranose isolated from cultures of *Curvularia eragrostidis* D2452.[1]

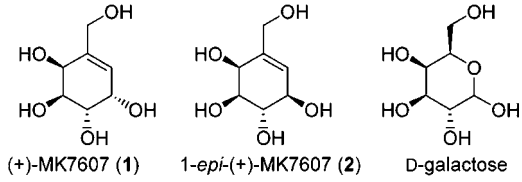


Figure 1. Structures of (+)-MK7607 (**1**) and its C-1 epimer **2**.

Structurally, it possesses four contiguous stereocenters, of which the absolute configurations are identical to those of α-galactose. Thus, this highly oxygenated cyclohexene compound could be considered a mimetic of α-galactose,[2] which is an important component in many biological processes.

The first total synthesis of racemic MK7607 was reported by Mehta in 2000,[3] and the synthesis of the non-natural enantiomer from (−)-shikimic acid was recorded by Singh in 2001.[4] However, the synthesis of the natural (+)-enantiomer has not been reported so far. The C-1 epimer of **1**, 1-*epi*-(+)-MK7607 (**2**), which could be regarded as a mimetic of *β*-galactose, was recently synthesized.[5] Very recently, the syntheses of 5-fluorinated analogues of **1** and **2** were also reported.[6]

As part of our ongoing research, we became interested in the structures of **1** and **2**, triggered by the fact that the latter

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(1) Nobuji, Y.; Noriko, C.; Takashi, M.; Shigeru, U.; Kenzou, H.; Michiaki, I. Jpn. Kokai Tokkyo Koho, JP, 06306000, 1994.

(2) (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (b) Arjona, O.; Gómez, A. M.; López, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919.

(3) Mehta, G.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3509.

(4) Song, C.; Jiang, S.; Singh, G. *Synlett* **2001**, 1983.

(5) Grondal, C.; Enders, D. *Synlett* **2006**, 3507.

(6) Sardinha, J.; Rauter, A. P.; Sollogoub, M. *Tetrahedron Lett.* **2008**, *49*, 5548.

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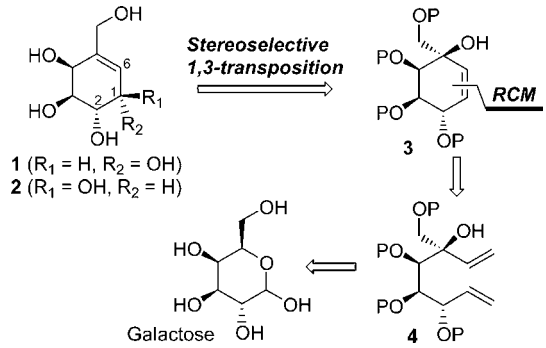
compound has a high affinity to a galactose-recognizing lectin.[7] We envisioned that the replacement of α- and β-galactose moieties of carbohydrate epitopes with their mimetics **1** and **2** could alter the inherent immunochemical properties of the epitopes.[8] In this regard, we undertook the synthesis of these carbasugars and their derivatives. Herein, we wish to report our efficient and stereoselective synthetic route to (+)-MK7607 (**1**) and its C-1 epimer **2** from a common intermediate.

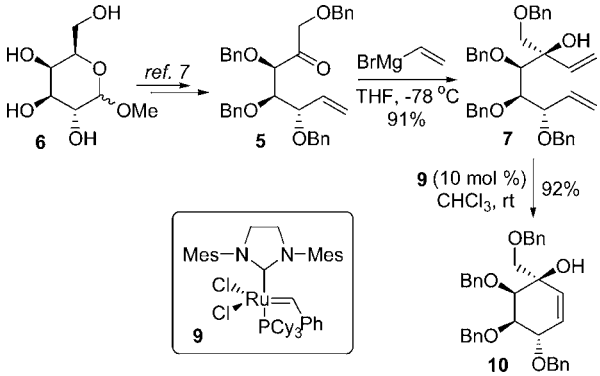
Our synthetic plan for the target molecules is outlined in Scheme 1. We envisaged that the C-1 stereocenters of **1** and **2** could be selectively introduced by the 1,3-transposition of the tertiary allylic hydroxyl group of **3**, although steric crowding around the tertiary hydroxyl group might limit the types of reactions applicable for this transformation. The cyclohexene ring of **3** would be constructed by a ring-closing metathesis (RCM) reaction of diene **4**. This diene **4** would arise from galactose, which bears the same absolute configurations at C-2, C-3, and C-4 as those in the final compounds **1** and **2**.

Scheme 1. Retrosynthetic Analysis of Compounds **1** and **2**



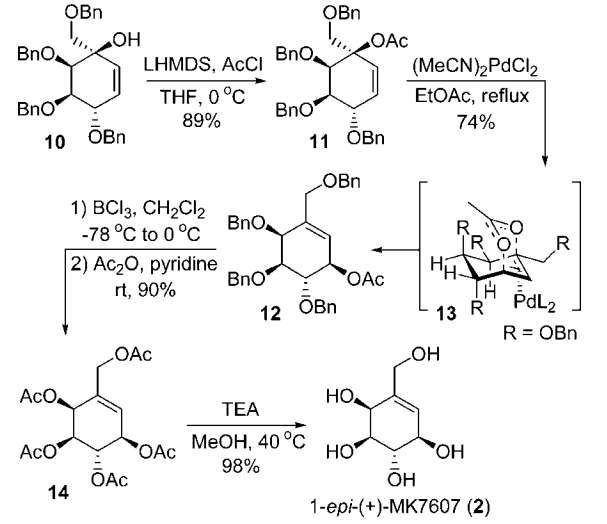
Our synthesis commenced with the preparation of the known ketone **5** from the commercially available galactose derivative **6**, according to the reported four-step procedures (Scheme 2).[9] Addition of vinylmagnesium bromide to ketone **5** in THF at −78 °C gave the RCM substrate **7** in 91% yield as the only detectable isomer. The stereochemistry of the newly generated stereocenter of **7** was tentatively assigned, as shown, on the basis of a chelation-controlled transition state model and established by its conversion to **8** (Scheme 4). The RCM of diene **7** was successfully performed with a second-generation Grubbs catalyst **9** in $CHCl_3$ at room temperature to produce the desired cyclohexene derivative **10** in 92% yield.

Scheme 2. Synthesis of Key Intermediate Cyclohexenol **10**



With a facile route to **10** in hand, our study first focused on the conversion of the tertiary allylic alcohol moiety of **10** to its transposed secondary allylic alcohol moiety of 1-*epi*-(+)-MK7607 (**2**). Toward this end,[10] we decided to utilize the allylic rearrangement of the allylic ester with palladium.[11] Thus, we examined the reaction of the tertiary allylic alcohol of **10** with an acylating agent to give tertiary allylic acetate **11**. The acetylation of **10** did not take place smoothly under normal reaction conditions, but it was found that treatment of **10** with LHMDS and acetyl chloride in THF successfully produced the desired acetate **11** in 89% yield (Scheme 3).

Scheme 3. Synthesis of 1-*epi*-(+)-MK7607 (**2**)



After investigating several reaction conditions for the allylic rearrangement of **11**, we found that treatment of **11** with a catalytic amount of $(MeCN)_2PdCl_2$ (10 mol %) in refluxing EtOAc led to the exclusive formation of the desired transposed secondary allylic acetate **12** in 74% yield. Under these reaction conditions, no trace of the C-1 α-isomer was detected in the crude ^1H NMR spectra. We established the relative configuration of **12** ultimately through its conversion

(7) Block, O. Dissertation, University of Wuppertal, Germany, 2000.

(8) (a) Peri, F.; Cipolla, L.; La Ferla, B.; Nicotra, F. *C. R. Chimica* **2003**, *6*, 635. (b) Schmieg, J.; Yang, G.; Franck, R. W.; Tsuji, M. *J. Exp. Med.* **2003**, *198*, 1631. (c) Tashiro, T.; Nakagawa, R.; Hirokawa, T.; Inoue, S.; Watarai, H.; Taniguchi, M.; Mori, K. *Tetrahedron Lett.* **2007**, *48*, 3343.

(9) Agrofoglio, L. A.; Amblard, F.; Nolan, S. P.; Charamon, S.; Gillaizeau, I.; Zevaco, T. A.; Guenot, P. *Tetrahedron* **2004**, *60*, 8397.

(10) All of our attempts to oxidize **10** to the transposed enone with a variety of reagents were unsuccessful, presumably because of the high degree of steric hindrance.

(11) (a) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *20*, 321. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

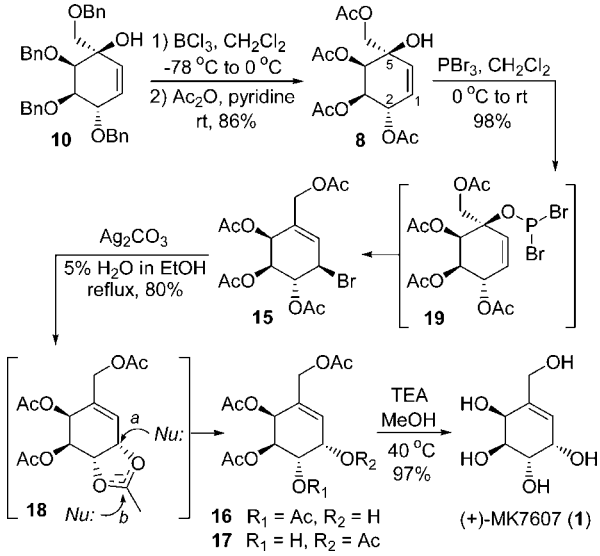
to final product **2**. The stereochemical outcome of this stereoselective allylic transposition could be rationalized by a [3,3]-sigmatropic reaction through transition state **13**, in which Pd(II) coordinates to the double bond on the less hindered α-face opposite the acetate group and facilitates the sigmatropic rearrangement on the β-face.[11b,12]

For the facile isolation of the hydrophilic final product **2**, the benzyl protecting groups of **12** were replaced with acetates to give pentaacetate **14** by treating **12** with BCl_3 and subsequent peracetylation in 90% overall yield. Finally, the desired 1-*epi*-(+)-MK7607 (**2**) was delivered in 98% yield upon treatment of **14** with triethylamine in MeOH and purification on a Dowex 50 (H^+) resin column. The spectroscopic data (^1H and ^{13}C NMR) and optical rotation for **2** were identical with those reported.[5]

Having achieved a selective synthesis of **2**, we turned our attention to the synthesis of (+)-MK7607 (**1**). We chose to utilize **10** as a common intermediate and exploit the route that would allow for the facile conversion to the final natural product **1**. Conceivably, the anti-S_N2' type substitution of the tertiary hydroxyl group of **10** by an oxygen nucleophile would provide a quick way to **1**. Thus, we investigated the feasibility of this transformation by using various reaction conditions including the Mitsunobu reaction.[13] Unfortunately, all attempts to bring about this transformation failed.

As an alternative approach for the desired transformation, we decided to utilize the Winstein's neighboring group participation of C-2 acetate.[14,15] To this end, the benzyl groups of **10** were replaced with acetates to give **8** in 86% overall yield (Scheme 4). The NOESY correlations of **8**

Scheme 4. Synthesis of (+)-MK7607 (**1**)



allowed the unequivocal assignment of the configuration of C-5.[16] With compound **8** in hand, efforts were directed to the activation of C-1 position by suprafacial allylic transposition. After some trials with several halogenating reagents, it was found that treatment of **8** with an excess of PBr_3 in CH_2Cl_2 led to the formation of the transposed allylic bromide **15**[17,18] as a single diastereomer in excellent yield (98%). On the basis of the analysis of the NOE data, the relative configuration of the newly introduced stereocenter was assigned as β.[16]

Heating the obtained β-bromide **15** in refluxing wet ethanol in the presence of Ag_2CO_3 afforded a 2:1 mixture of inseparable acetates **16** and **17** in 80% combined yield. The formation of both acetates **16** and **17**, as well as the configurational inversion of C-1, suggested that this reaction involves the oxonium ion intermediate **18**, which collapses via path *b* but not via path *a*.[14,19] Finally, removal of the acetate groups in **16** and **17** with triethylamine in MeOH and purification on a Dowex 50 (H^+) resin column gave (+)-MK7607 (**1**), whose $[\alpha]_D$ value and other spectra were in agreement with those reported.[1]

In this synthetic process, particularly worthy of note is the stereospecific PBr_3-mediated allylic-transposed bromination of the tertiary allylic alcohol **8**. It is known that halogenation of tertiary allylic alcohols with PBr_3 leads to the transposed allylic bromides, and generally believed that this transformation involves intra- or intermolecular attack of the phosphate ester intermediate by bromide.[20] To our knowledge, only a few precedents exist for the cyclic systems, but the stereochemistry of the rearranged products was ambiguously determined.[21] Although more systematic studies are needed to elucidate the origin of the observed selective stereochemical outcome of **15**, we suggest that it could be a result of the S_Ni' reaction mechanism of intermediate phosphate ester **19**. This mechanistic assumption could be substantiated as follows.

To examine the possible stereodirecting effect of the C-2 acetoxyl group via anchimeric assistance, the nonanchimeric

(12) (a) Yuasa, Y.; Yuasa, Y. *Synth. Commun.* **2006**, *36*, 1671. (b) Inomata, K.; Murata, Y.; Kato, H.; Tsukahara, Y.; Kinoshita, H.; Kotake, H. *Chem. Lett.* **1985**, 931.

(13) For related attempts, see: (a) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J.-N. *J. Am. Chem. Soc.* **2002**, *124*, 5380. (b) Young, J.-j.; Jung, L.-j.; Cheng, K.-m. *Tetrahedron Lett.* **2000**, *41*, 3411.

(14) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2780.

(15) For representative examples, see: (a) Davies, S. G.; Long, M. J. C.; Smith, A. D. *Chem. Commun.* **2005**, 4536. (b) Pei, Z.; Dong, H.; Ramström, O. *J. Org. Chem.* **2005**, *70*, 6952.

(16) See Supporting Information for details.

(17) The synthesis of the enantiomer of bromide **15** as a mixture with its C-1 isomer was previously reported, see: (a) Ogawa, S.; Hattori, T.; Toyokuni, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2077. (b) Ogawa, S.; Sakata, Y.; Ito, N.; Watanabe, M.; Kabayama, K.; Itoh, M.; Korenaga, T. *Bioorg. Med. Chem.* **2004**, *12*, 995.

(18) Contrary to a report that bromide 15 is unstable (see ref 17), the pure bromide 15 proved to be fairly stable in our hands.

(19) Woodward, R. B.; Brutcher, F. V., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 209.

(20) For representative examples in an acyclic system, see: (a) Babler, J. H. *J. Org. Chem.* **1976**, *41*, 1262. (b) Bakkestuen, A. K.; Gundersen, L.-L.; Petersen, D.; Utenova, B. T.; Vik, A. *Org. Biomol. Chem.* **2005**, *3*, 1025.

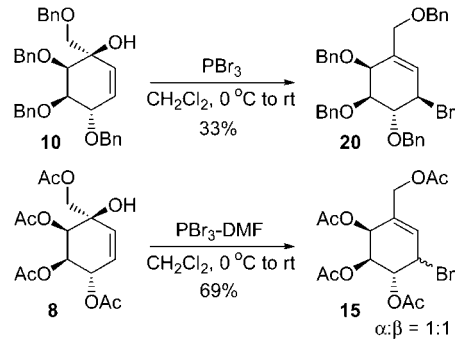
(21) (a) Zhang, A.; Csutoras, C.; Zong, R.; Neumeyer, J. L. *Org. Lett.* **2005**, *7*, 3239. (b) Nampalli, S.; Bhide, R. S.; Nakai, H. *Synth. Commun.* **1992**, *22*, 1165.

(22) (a) Robin, J.-P.; Landais, Y. *Tetrahedron* **1992**, *48*, 819. (b) Ramage, R.; Griffiths, G. J.; Shutt, F. E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1539.

(23) (a) Yajima, T.; Munakata, K. *Chem. Lett.* **1977**, 891. (b) Koganty, R. R.; Shambhu, M. B.; Digenis, G. A. *Tetrahedron Lett.* **1973**, *14*, 4511.

benzyl group containing alcohol **10** was subjected to the same reaction conditions (Scheme 5). The reaction produced the

Scheme 5. Allylic-Transposed Bromination of Compounds **10** and **8**



C-1 β-bromide **20** as the only product isolated albeit in low yield (33%). The low yield of **20** could be attributed to the instability of the benzyl protecting groups under the reaction conditions.[22] This result suggested that the anchimeric assistance of the C-2 acetoxyl group of **8** might not be a major contributing factor in determining the selectivity in the formation of **15**.

If the bromination reaction proceeds via intermolecular attack of bromide ion, the sole formation of **15** is unlikely, regardless of the involvement of anchimeric assistance. When the anchimeric assistance of the C-2 acetoxyl group was involved in the intermolecular mechanism, the reaction would proceed through the oxonium ion intermediate **18** (Scheme 4), and the bromide product **15** would be formed by attack of bromide ion at C-1 (path *a*).

In this case, the C-1 oxygenated product might be formed also, at least as a minor byproduct, upon competitive collapse of the oxonium ion intermediate (path *b*).[14,15] However, no trace of the C-1 oxygenated product was detected in the crude ^{1}H NMR spectra. This observation implied that the intermolecular mechanism involving oxonium ion might not be a preferred pathway. In the case where the carbocation intermediate was involved in the intermolecular mechanism, a high selectivity would not be expected based on steric and stereoelectronic considerations. To support these notions, we treated compound **8** in CH_2Cl_2 with the complex of PBr_3 with DMF as a brominating agent that was proposed to exist as an iminium bromide salt and undergo a bromination reaction via a stepwise intermolecular mechanism.[21b,23] As expected, the reaction of **8** gave an inseparable 1:1 mixture of the transposed allylic bromide **15** and its C-1 α-isomer in 69% combined yield (Scheme 5). All of the above results indirectly supported that the S_Ni' mechanism might be a plausible explanation for the stereochemical outcome of **15**.

In conclusion, here we describe an efficient and selective synthetic route to (+)-MK7607 (**1**) and its C-1 epimer **2** from a readily obtainable intermediate **10** in high overall yields. An important feature of this synthesis was the stereospecific 1,3-allylic transposition of the hindered tertiary alcohol group of compound **10**. For this conversion, the palladium-catalyzed allylic transposition reaction and the PBr_3-mediated allylic-transposed bromination reaction were employed. The synthetic process was highly selective and efficiently provided synthetically useful intermediates particularly in the preparation of MK7607-containing analogues.

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Supporting Information Available: Experimental procedures, product characterization, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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