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Novel Sequential Sigmatropic Rearrangements of Allylic Diols: Application to the Total Synthesis of (−)-Kainic Acid

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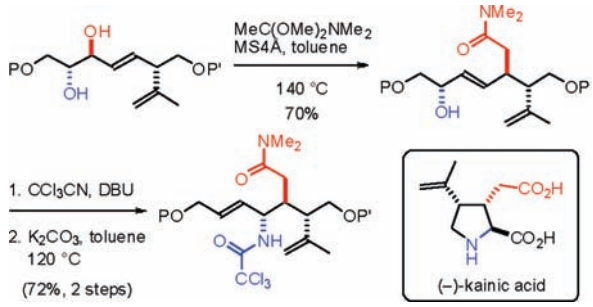
ABSTRACT



Sequential sigmatropic rearrangements (Claisen/Claisen and Claisen/Overman) of enantiopure allylic diols are described. The reactions proceeded in complete diastereoselectivity without protecting group manipulations. The sequential Claisen/Overman rearrangement was successfully applied to the total synthesis of (−)-kainic acid.

Chirality transfer through [3,3]-sigmatropic rearrangements is one of the most reliable approaches for accessing enantiopure multifunctional molecules.[1] Stereochemical information embedded in an optically pure allylic alcohol can be transferred to newly generated carbon−carbon or carbon−heteroatom bonds in a highly diastereoselective fashion. Promising diastereoselectivity can be observed even in a flexible acyclic system because of the organized six-membered transition state.

To maximize the potential utility of chirality transfer through [3,3]-sigmatropic rearrangements, our laboratory has been attracted to sequential sigmatropic rearrangements of enantiopure 1,2-allylic diols **1**,[2] which can be readily prepared via a number of methods, such as Sharpless asymmetric dihydroxylation[3] and use of naturally occurring monosaccarides and tartaric acid. The realization of two types of novel sequential sigmatropic rearrangements is outlined in Scheme 1. In the sequential Claisen/Claisen rearrangement (**1**→**2**→**3**), the first rearrangement of allylic diol **1** would generate **2**,[4,5] which would then spontaneously undergo the second rearrangement to give bisamide **3**. The reaction would

(1) For selected reviews on chirality transfer through sigmatropic rearrangemetnt, see: (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882. (b) Nubbemeyer, U. *Synthesis* **2003**, 961–1008.

(2) For selected recent reviews on cascade, tandem, and domino reactions including sigmatropic rearrangements, see: (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619–1665. (c) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341–5378. (d) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092–3101. (e) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133–3148.

(3) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345–1376.

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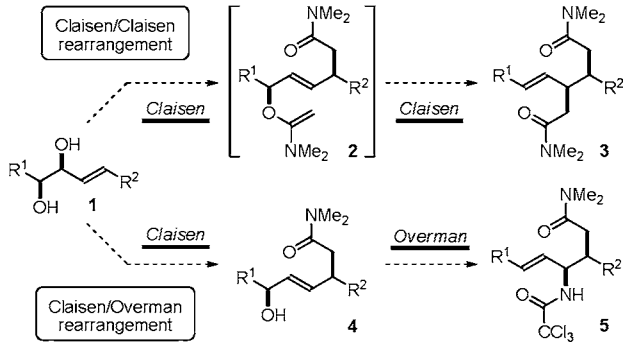
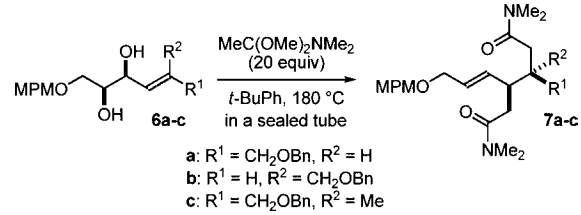
Scheme 1. Two Types of Sequential Sigmatropic Rearrangements



proceed in one pot and install two identical functional groups. On the other hand, the sequential Claisen/Overman rearrangement (**1**→**4**→**5**) would introduce two different functional groups.[6] This transformation is more challenging because it requires the suppression of the second competitive Claisen rearrangement (**4**→**2**→**3**) following the first transformation.[7] If the single rearrangement of **1** can be completely controlled, however, a variety of sigmatropic rearrangements, including the Overman rearrangement (**4**→**5**),[8,9] could be subsequently applied to the resultant allylic alcohol. To synthesize **3** and **5** by classical sigmatropic rearrangements, protection of the homoallylic alcohol in **1** is required prior to the first rearrangement, with the second reaction performed after deprotection. However, our proposed sequential methods would preclude protecting group manipulation. In addition, the expected high diastereoselectivities through the tight chairlike transition states would be an attractive advantage in these sequential reactions.

Our studies of the sequential Claisen/Claisen rearrangement commenced with enantiopure *E*-allylic *syn*-diol **6a** derived from tartaric acid (Table 1). As we expected,

Table 1. Sequential Claisen/Claisen Rearrangements of Allylic Diols **6a**−**c**[a]



a: $R^1 = CH_2OBn$, $R^2 = H$
b: $R^1 = H$, $R^2 = CH_2OBn$
c: $R^1 = CH_2OBn$, $R^2 = Me$

entry	diol	time (d)	product	yield (%)
1	**6a**	2	**7a**	87
2	**6b**	2	**7b**	81
3	**6c**	2.5	**7c**	66

[a] Conditions: 55 μmol of **6**, 20 equiv of $MeC(OMe)_2NMe_2$, *t*-BuPh (0.03 M), 180 °C in a sealed tube.

Eschenmoser's conditions with excess $MeC(OMe)_2NMe_2$ at 180 °C in a sealed tube provided **7a** in 87% yield (entry 1).[10] The reaction proceeded diastereoselectively, with **7a** isolated as the sole product. High stereoselection was also observed in the reaction of *Z*-allylic *syn*-diol **6b** to give **7b** in 81% yield (entry 2). Because both enantiomers of the *syn*-diols are readily available, all possible stereoisomers of **7** can be synthesized by choosing the appropriate combinations of the diol stereochemistry and the olefin geometry. The sequential rearrangement of the trisubstituted olefin **6c** enabled us to construct two contiguous stereocenters including a highly congested quaternary carbon (entry 3).

Having successfully developed the sequential Claisen/Claisen rearrangement, we turned our attention to the more challenging Claisen/Overman version (Table 2). To circumvent the inherent problem of overreaction after the first rearrangement (Scheme 1, **4**→**2**→**3**), we envisioned the first Claisen rearrangement via cyclic orthoamides.[11] Addition of 1 equiv of $MeC(OMe)_2NMe_2$ to a solution of diol **6a** and *o*-xylene led to the formation of cyclic orthoamide **8a** at room temperature (entry 1). The resulting orthoamide **8a** was then heated to 160 °C in the same reaction vessel to furnish the singly rearranged product **10a** through *N*,*O*-ketene acetal **9a** in 16% yield, along with recovery of starting material **6a**. Although use of 2 equiv of $MeC(OMe)_2NMe_2$ increased

(4) For selected reviews on Claisen rearrangements, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002. (b) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597–643.

(5) We reported the formal synthesis of (−)-morphine using the Claisen/Claisen rearrangement of a cyclic allylic diol; see: (a) Tanimoto, H.; Saito, R.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 358–362. For selected examples of Claisen/Claisen rearrangements except for an aromatic version, see: (b) Curran, D. P.; Suh, Y.-G. *Carbohydr. Res.* **1987**, *171*, 161–191.

(6) For selected examples of sequential reactions including Claisen rearrangements, see: (a) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91*, 3281–3289. (b) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1611–1612. (c) Raucher, S.; Burks, J. E., Jr.; Hwang, K.-J.; Svedberg, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 1853–1855. (d) Mikami, K.; Taya, S.; Nakai, T.; Fujita, Y. *J. Org. Chem.* **1981**, *46*, 5447–5449. (e) Mulzer, V. J.; Bock, H.; Eck, W.; Buschmann, J.; Luger, P. *Angew. Chem.* **1991**, *103*, 450–452. (f) Posner, G. H.; Carry, J.-C.; Crouch, R. D.; Johnson, N. *J. Org. Chem.* **1991**, *56*, 6987–6993. (g) Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371–1374. (h) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569–8575. (i) Pelc, M. J.; Zakarian, A. *Org. Lett.* **2005**, *7*, 1629–1631. (j) Li, X.; Ovaska, T. V. *Org. Lett.* **2007**, *9*, 3837–3840. (k) Ilardi, E. A.; Isaacman, M. J.; Qin, Y.-C.; Shelly, S. A.; Zakarian, A. *Tetrahedron* **2009**, *65*, 3261–3269.

(7) Curran reported the single Claisen rearrangement of an allylic bisketenesilylacetal; see ref 5b.

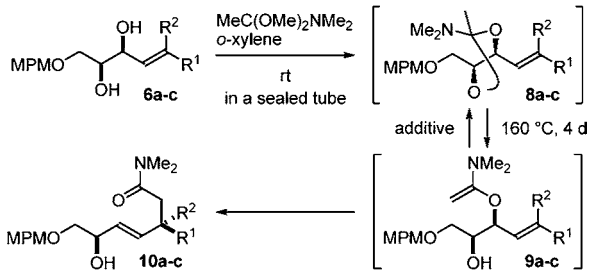
(8) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597–599. For reviews on Overman rearrangements, see: (b) Overman, L. E.; Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, NY, 2005; Vol. 66, pp 1−107.

(9) We reported a sequential Overman/Overman rearrangement in the total syntheses of biologically active compounds; see: (a) Momose, T.; Hama, N.; Higashino, C.; Sato, H.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 1376–1379. (b) Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett.* **2009**, *11*, 2687–2690. For selected examples of sequential reactions including Overman rearrangements, see: (c) Villemin, D.; Hachemi, M. *Synth. Commun.* **1996**, *26*, 1329–1334. (d) Banert, K.; Fendel, W.; Schlott, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3289–3292. (e) Demay, S.; Kotschy, A.; Knochel, P. *Synthesis* **2001**, 863–866. (f) Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067–3070.

(10) Stereochemistries of **7a**−**c** and **11a**−**c** were established through their cyclic derivatives and subsequent NOE experiments; see the Supporting Information.

(11) Overman rearrangements through cyclic orthoamides were reported; see: (a) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037–2039. (b) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829–4837.

Table 2. Claisen Rearrangement of Allylic *syn*-Diols **6a**−**c** through Cyclic Orthoamides **8a**−**c**[a]

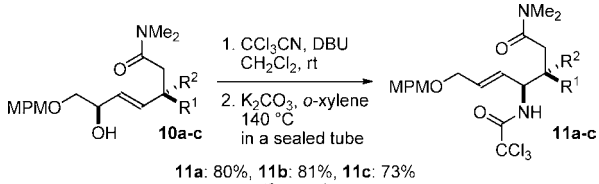


				yield (%)	
entry	diol	$MeC(OMe)_2NMe_2$(equiv)	additive	**10**	**7**
1	**6a**	1.0	none	16	0
2	**6a**	2.0	none	52	9
3	**6a**	2.0	MS4 Å	91	0
4	**6b**	2.0	MS4 Å	89	0
5	**6c**	2.0	MS4 Å	95	0

[a] Conditions: 140 μmol of **6**, $MeC(OMe)_2NMe_2$, *o*-xylene (0.03 M), rt, then MS4 Å (0 or 500 wt %), 160 °C in a sealed tube.

the yield, doubly rearranged product **7a** was concomitantly generated because of the presence of the excess $MeC(OMe)_2NMe_2$ (entry 2). After an extensive survey of methods to suppress the double rearrangement, we finally found that the addition of 500 wt % MS4Å to orthoamide **8a** prior to heating was critical for obtaining **10a** in 91% yield (entry 3).[12] The developed procedure through the cyclic orthoamide was reliable. The reaction of *Z*-allylic *syn*-diol **6b** and trisubstituted olefin **6c** gave allylic alcohols **10b** and **10c** in 89% and 95% yield, respectively (entries 4 and 5). We then demonstrated the Overman rearrangement of the resulting allylic alcohols **10a**−**c** (Scheme 2). Allylic alcohols

Scheme 2. Overman Rearrangement of Allylic Alcohols **10a**−**c**



11a: 80%, **11b**: 81%, **11c**: 73% (2 steps)

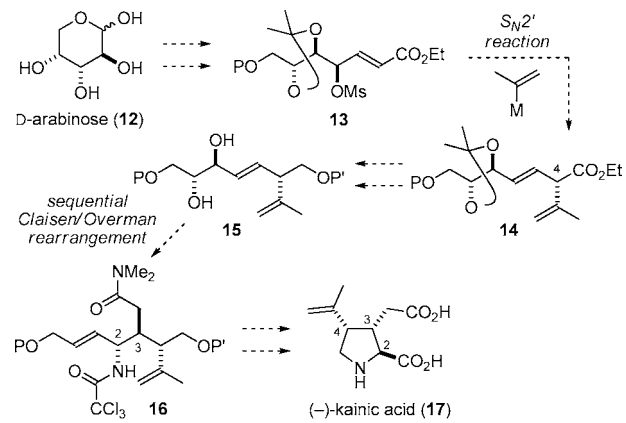
10a−**c** were transformed to trichloroimidates, which were subsequently heated in the presence of K_2CO_3[13] to give trichloroacetamide **11a**−**c** in 73−81% yields over two steps.[10]

(12) We believe that MS4Å may selectively decompose the excess $MeC(OMe)_2NMe_2$ in the presence of cyclic orthoamide **8a**. In fact, when MS4Å is added at the beginning of the reaction, the formation of the orthoamide is suppressed.

(13) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188–192.

To demonstrate the practical utility of the sequential sigmatropic rearrangements, we applied this methodology in the synthesis of (−)-kainic acid (**17**),[14] which was isolated from the Japanese marine alga *Digenea simplex*.[15,16] Kainic acid was originally used in anthelmintic and insecticide preparations[17] and recently has been applied to the study of neuropharmacology because of its ability to cause responses that mimic neuronal disorders, such as Alzheimer's disease.[18] A conspicuous feature of our approach to kainic acid is the use of chirality transfer in acyclic compounds made possible by taking advantage of the three secondary hydroxy groups embedded in D-arabinose (Scheme 3). An S_N2' reaction

Scheme 3. Synthetic Plan toward (−)-Kainic Acid (**17**)



(**13**→**14**) and sequential Claisen/Overman rearrangements (**15**→**16**) could establish all of the chiral stereocenters (C2, C3, C4) in kainic acid.

The synthesis of (−)-kainic acid (**17**) commenced with selective MOM protection of **18**, which was prepared from

(14) For selected reviews on the Kainoid family, see: (a) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149–4174. (b) Moloney, M. G. *Nat. Prod. Rep.* **1998**, *15*, 205–219. (c) Moloney, M. G. *Nat. Prod. Rep.* **1999**, *16*, 485–498. (d) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597–616.

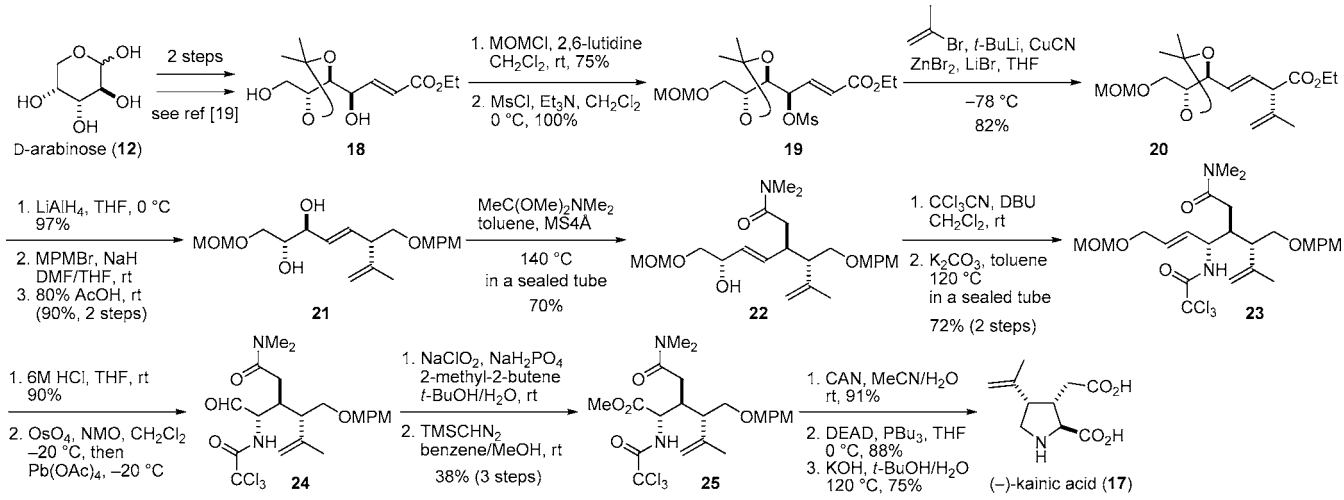
(15) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026–1028.

(16) For recent examples of the enantioselective total synthesis of kainic acid, see: (a) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727–4733. (b) Martinez, M. M.; Hoppe, D. *Org. Lett.* **2004**, *6*, 3743–3746. (c) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763–4776. (d) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045–3047. (e) Anderson, J. C.; O'Loughlin, J. M. A.; Tornos, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2741–2749. (f) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2005**, *7*, 4337–4340. (g) Poisson, J.-F.; Orellana, A.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 10860–10863. (h) Pandey, S. K.; Orellana, A.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 5665–5668. (i) Sakaguchi, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 1635–1638. (j) Chalker, J. M.; Yang, A.; Deng, K.; Cohen, T. *Org. Lett.* **2007**, *9*, 3825–3828. (k) Jung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, K. S.; Jung, K. W. *J. Org. Chem.* **2007**, *72*, 10114–10122. (l) Sakaguchi, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1711–1714. (m) Tomooka, K.; Akiyama, T.; Man, P.; Suzuki, M. *Tetrahedron Lett.* **2008**, *49*, 6327–6329. (n) Farwick, A.; Helmchen, G. *Org. Lett.* **2010**, *12*, 1108–1111.

(17) Nitta, I.; Watase, H.; Tomiie, Y. *Nature* **1958**, *181*, 761–762.

(18) (a) MacGeer, E. G.; Olney, J. W.; MacGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven: New York, 1978. (b) Goodenough, S.; Schleusner, D.; Pietrzik, C.; Skutella, T.; Behl, C. *Neuroscience* **2005**, *132*, 581–589. (c) Abdul, H. M.; Sultana, R.; Keller, J. N.; Clair, D. K. S.; Markesbery, W. R.; Butterfield, D. A. *J. Neurochem.* **2006**, *96*, 1322–1335.

Scheme 4. Total Synthesis of (−)-Kainic Acid (**17**) through the Sequential Claisen/Overman Rearrangement



D-arabinose by a known two-step sequence (Scheme 4).[19] The remaining secondary alcohol was converted to the mesylate. In the next S_N2' reaction of γ-mesyloxy α,β-enoate **19**, we modified the original conditions reported by Ibuka and Yamamoto to give **20** in 82% yield in a stereo- and regioselective manner.[20] *E*-Allylic *anti*-diol **21** was then synthesized from ethyl ester **20** via a three-step sequence involving $LiAlH_4$ reduction, MPM protection, and removal of the acetonide. The stage was now set for the crucial sequential Claisen/Overman rearrangement. Both the Claisen rearrangement of **21** and the subsequent Overman rearrangement proceeded with complete diastereoselectivity, affording trichloroacetamide **23**. Thus, we successfully installed all stereocenters present in kainic acid in the acyclic intermediate through three chirality transfer reactions

With the key acyclic intermediate **23** in hand, we turned our attention to the chemoselective oxidative cleavage of *trans*-olefin **23**. After removal of the MOM group, a hydroxy-directed dihydroxylation under anhydrous conditions[21] followed by addition of $Pb(OAc)_4$ gave aldehyde **24** without touching the exomethylene group. Kraus−Pinnick oxidation followed by methylation of the acid then provided methyl ester **25** in 38% yield (3 steps). The pyrrolidine structure was constructed by cleavage of the PMB group with CAN, followed by a Mitsunobu reaction.[22] Global deprotection with KOH in *t*-BuOH/H_2O at 120 °C accomplished the total synthesis of (−)-kainic acid (**17**). Our sample was found to be indistinguishable from the natural product on the basis of ^{1}H NMR, ^{13}C NMR, HRMS, IR, MP, and its optical rotaion.

In summary, we developed two novel sequential sigmatropic rearrangements of optically pure allylic diols. The reactions proceed in high yields with complete diastereoselectivity. By choosing appropriate reaction conditions, two identical functional groups (Claisen/Claisen) or two different groups (Claisen/Overman) can be installed from the same allylic diols without protecting group manipulation. In particular, an orthoamide-type Claisen rearrangement developed in the Claisen/Overman sequence is very useful because a variety of sigmatropic rearrangements can be employed in the second rearrangement. As a demonstration of the sequential Claisen/Overman rearrangement, we achieved the total synthesis of (−)-kainic acid through three chirality transfers, taking advantage of the secondary hydroxy groups in D-arabinose.

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

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(20) (a) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864–4872. (b) Habashita, H.; Kawasaki, T.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 2392–2396.

(21) (a) Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399–3402. (b) Smith, A. B., III; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217–1226. (c) Donohoe, T. J.; Garg, R.; Moore, P. R. *Tetrahedron Lett.* **1996**, *37*, 3407–3410.

(22) For the Mitsunobu reaction of trichloroacetamides to synthesize 2-oxazolines, see: Roush, D. M.; Patel, M. M. *Synth. Commun.* **1985**, *15*, 675–679.