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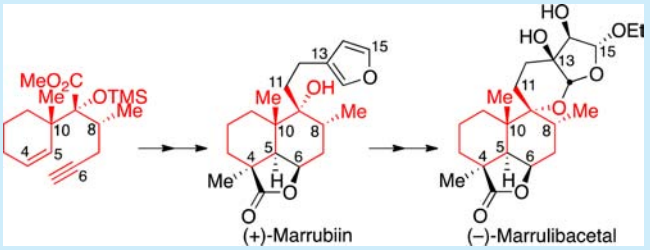
Total Syntheses of (+)-Marrubiin and (−)-Marrulibacetal

Hiroyuki Yamakoshi, Yuki Sawayama, Yoshihiro Akahori, Marie Kato, and Seiichi Nakamura*

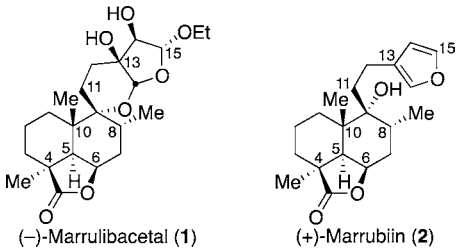
Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

Supporting Information

ABSTRACT: A stereoselective total synthesis of (+)-marrubiin has been accomplished starting from a chiral building block via the $CyNH_2$-promoted Pauson−Khand reaction (PKR) followed by oxidative cleavage of the resultant cyclopentenone ring. Two successive oxidations and internal transacetalization culminated in the total synthesis of the antispasmodic labdane diterpenoid (−)-marrulibacetal.



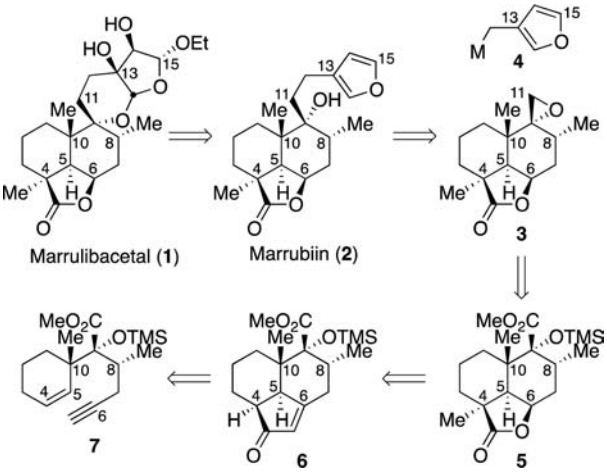
In 2009, Borrelli and co-workers isolated and characterized a labdane diterpenoid marrulibacetal (**1**) from the aerial parts of *Marrubium globosum* ssp. *libanoticum*, a medicinal plant used as hypoglycemic, febrifuge, antispasmodic, and anti-inflammatory drugs in Northern Lebanon.[1] Due to its antispasmodic effects in the isolated mouse ileum, this natural product is considered to be the active ingredient of the herb. The structure of **1** was determined on the basis of NMR spectroscopic data. Since **1** was also obtained from *Marrubium deserti de Noé* that produces marrubiin (**2**),[2,3] the bitter principle of horehound, **1** is speculated to be biosynthesized through oxidation of **2**, though there is no evidence to support this speculation.



As part of our studies on the synthesis of biologically active natural products, we have recently developed stereocontrolled methods to access chiral building blocks for oxygenated terpenoids by exploiting an Ireland−Claisen rearrangement.[4] To demonstrate the synthetic utility of these building blocks, we addressed the synthesis of **1** via its presumed biosynthetic precursor **2**.[5]

As outlined in Scheme 1, we planned to introduce the furan moiety late in the synthesis, because the implementation of this strategy would allow the incorporation of a variety of substituents into a common, fully elaborated intermediate **3**,[6] which would be accessible from ester **5** through a chemoselective reduction. Comparison of the structure of lactone **5** to that of chiral building block **7** revealed that, in addition to the installation of a methyl group at C4 by an enolate alkylation from the less-hindered diastereoface, both carboxylation at C4

Scheme 1. Retrosynthetic Analysis of Marrulibacetal (1) and Marrubiin (2)



and oxidative cleavage of the C−C bond at C6 were required, together with the C5−C6 bond formation. We therefore decided to utilize a Pauson−Khand reaction (PKR)/oxidative cleavage sequence to achieve this transformation.

While PKR[7,8] has been utilized for the construction of a dodecahydroacenaphthylene skeleton,[9,10] there has been no report on the formation of [6,6]-*trans*-fused compounds. Therefore, we converted enyne **7** to the corresponding dicobalt complex **8** ($Co_2(CO)_8$, CH_2Cl_2, 97% yield) and examined several conditions to achieve the desired transformation (Table 1). Since initial attempts to carry out the intramolecular reaction in refluxing MeCN resulted in decomplexation (entry 1), we were prompted to investigate the effect of promoters. As expected, the desired tricyclic product **6** was obtained as a single isomer when using NMO, a representative and well-established promoter for PKR,[11] in CH_2Cl_2 at room temper-

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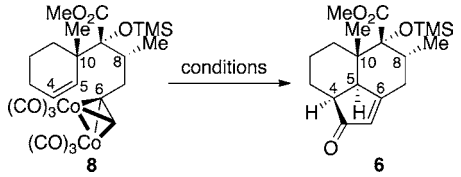
Table 1. PKR of Dicobalt Complex 8



entry	additive	solvent	concn (mM)	temp	time (h)	yield (%)
1	none	MeCN	7	reflux	0.5	0[a]
2	NMO	CH_2Cl_2	20	rt	2	23[a]
3	$CyNH_2$	$(CH_2Cl)_2$	30	reflux	2	71
4	$CyNH_2$	$(CH_2Cl)_2$	10	reflux	1.5	97

[a]Enyne **7** was obtained.

ature, although the yield (23%) suffered due to competitive decomplexation (entry 2). The 4,5-*cis*-5,10-*trans* relationship for the product **6** was unambiguously established by a NOESY experiment (Figure 1). After considerable experimentation with

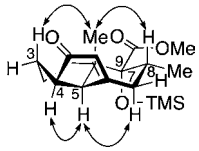
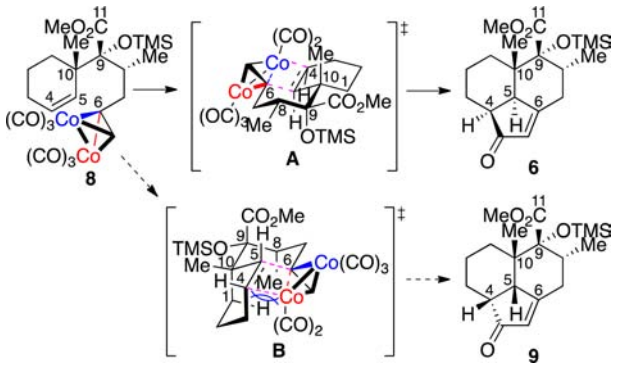


Figure 1. Relevant NOESY data for enone **6**.

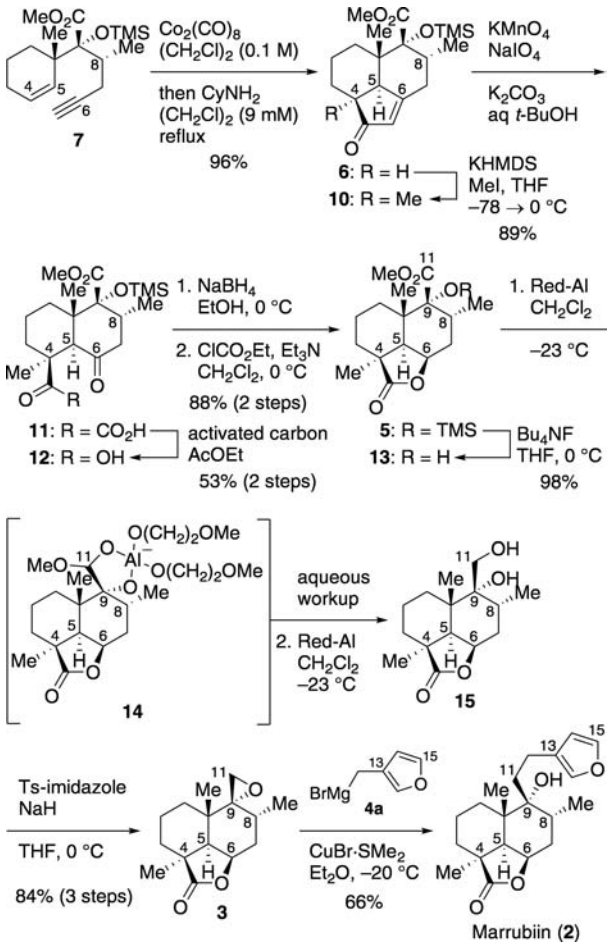
other promoters, we were gratified to find that cyclohexylamine, the effectiveness of which was introduced by Sugihara and Yamaguchi and co-workers,[12] was a promoter of choice for this transformation, providing enone **6** in 71% yield (entry 3). The chemical yield was further improved to 97% by decreasing the substrate concentration from 30 to 10 mM in order to prevent intermolecular reaction (entry 4). With regard to the reaction pathway of PKR, Magnus and Principe suggested a working model in 1985,[13] and results of quantum mechanical studies were later reported by Nakamura and Yamanaka.[14] Based on the results of density functional studies, it was concluded that the stereochemistry of PKR is determined by the irreversible olefin insertion step. In this case, it is speculated that the reaction did not proceed through *cis*-fused chair−chairlike TS **B**, which suffers from severe steric interaction between C1−H and C8-Me (Scheme 2). No such nonbonded destabilization was observed in *trans*-fused chair−boatlike TS **A**, thus leading to the exclusive formation of isomer **6**.

Scheme 2. Stereochemical Course of PKR of 8



Having optimized the reaction conditions for PKR, we then addressed the synthesis of **2** (Scheme 3). Since the formation of

Scheme 3. Total Synthesis of (+)-Marrubiin



dicobalt complex **8** could be carried out in the same solvent as that used for PKR, a convenient one-pot procedure was devised: treatment of enyne **7** with $Co_2(CO)_8$ in $(CH_2Cl)_2$ at room temperature was followed by addition of cyclohexylamine, 11-fold dilution with $(CH_2Cl)_2$, and heating under reflux. By utilizing this procedure, tricyclic enone **6** was obtained in comparable (96%) yield. *C*-Alkylation of the potassium enolate, generated from **6** with KHMDS in THF, with MeI proceeded in a stereoselective manner to give enone **10** in 89% yield. At this stage, we were challenged with the task of oxidative cleavage of the cyclopentenone moiety. In this regard, $RuCl_3$-catalyzed oxidation,[15] a dihydroxylation/oxidative cleavage sequence,[16] or ozonolysis/oxidative workup[17] is employed in the literature. However, Ru-catalyzed oxidation of enone **10** at room temperature resulted in the formation of a complex mixture of products, whereas OsO_4-catalyzed dihydroxylation did not proceed even at elevated temperatures. While desired ketocarboxylic acid **12** was obtained by ozonolysis of enone **10** with oxidative workup (O_3, CH_2Cl_2, −78 °C; NaOH, 30% aq H_2O_2), the reaction suffered from low yield (33%) and reproducibility issues. Finally, the desired transformation could be effected in 53% overall yield when subjected to $KMnO_4$-catalyzed oxidation in the presence of $NaIO_4$ and subsequent treatment of the resultant α-ketocarboxylic acid **11** with activated carbon.[18] Following the

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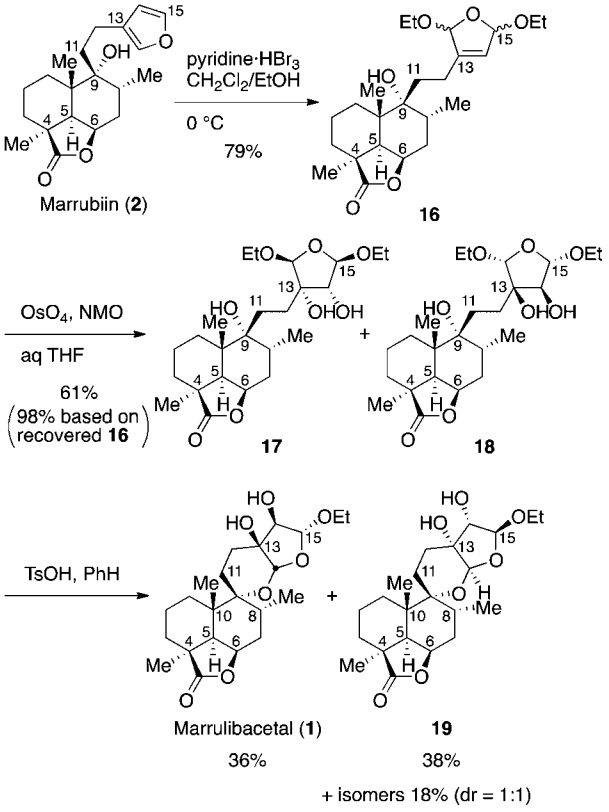
literature precedent,[5] ketocarboxylic acid **12** thus obtained was converted into lactone **5** by a two-step sequence involving reduction with $NaBH_4$ and lactonization through a mixed anhydride.

With the route to tricyclic lactone **5** secured, remaining operations necessary for the synthesis of marrubiin involved chemoselective reduction of the C11 ester functionality and introduction of a furan moiety. The TMS ether at C9 was deprotected by Bu_4NF in THF at 0 °C in preparation for hydroxyl-directed reduction. After a survey of reducing agents, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) proved to be the optimal reagent for this purpose. Thus, Red-Al reduction of α-hydroxyester **13** in CH_2Cl_2 at −23 °C followed by aqueous workup afforded a mixture of the corresponding aldehyde and diol **15**, which was reduced again with Red-Al to give diol **15**. This result can be rationalized by assuming the formation of a five-membered aluminate intermediate **14**. Treatment of diol **15** with Ts-imidazole and NaH afforded epoxide **3** in 84% yield for the three-step sequence. Epoxide ring opening with (3-furylmethyl)magnesium bromide[6] in the presence of CuBr·SMe_2 in Et_2O at −20 °C completed the total synthesis of (+)-**2**.

With optically active marrubiin in hand, we could then focus on the conversion of (+)-**2** to marrulibacetal (Scheme 4).

Scheme 4. Conversion of (+)-Marrubiin to (−)-Marrulibacetal



Exposure of (+)-**2** to pyridine tribromide in CH_2Cl_2/EtOH effected oxidative acetalization to provide bisacetal **16** as a 2:1 mixture of *cis* and *trans* diastereomers in 79% yield. It was somewhat surprising that internal acetalization did not occur under these conditions, probably due to the conformationally constrained *trans*-decalin moiety.[19,20] As speculated from literature precedents,[21] the *cis*-isomers *cis*-**16** could be osmylated selectively over the *trans*-isomers *trans*-**16** in aqueous THF, providing a 1:1 diastereomeric mixture of *cis*-diols **17** and **18** in 61% yield. Alkene **16**, recovered unchanged in 38% yield, could be recycled back to a 2:1 mixture of isomers by isomerization under acidic conditions (PPTS, EtOH, 90% yield). Internal transacetalization of *cis*-diols **17** and **18** could be attained with TsOH in undried benzene, providing (−)-marrulibacetal (**1**) in 36% yield, along with its isomer **19** (38% yield) and other two diastereomers (1:1, 18% combined yield).[22] Synthetic compounds proved to be identical in all respects (^1H and ^{13}C NMR, IR, HRMS, and optical rotations) to natural products.[1,23]

In conclusion, total syntheses of both (+)-marrubiin and (−)-marrulibacetal have been accomplished. The syntheses illustrate the synthetic utility of chiral building blocks developed in our laboratory for the synthesis of oxygenated terpenoids. The synthesis will open entries into analogues for biological investigations, leading to a useful structure−activity relationship.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01602.

Experimental procedures and full characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nakamura@phar.nagoya-cu.ac.jp.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Rigano, D.; Aviello, G.; Bruno, M.; Formisano, C.; Rosselli, S.; Capasso, R.; Senatore, F.; Izzo, A. A.; Borrelli, F. *J. Nat. Prod.* **2009**, *72*, 1477−1481.

(2) Zaabat, N.; Hay, A.-E.; Michalet, S.; Darbour, N.; Bayet, C.; Skandrani, I.; Chekir-Ghedira, L.; Akkal, S.; Dijoux-Franca, M.-G. *Food Chem. Toxicol.* **2011**, *49*, 3328−3335.

(3) Popoola, O. K.; Elbagory, A. M.; Ameer, F.; Hussein, A. A. *Molecules* **2013**, *18*, 9049−9060.

(4) Akahori, Y.; Yamakoshi, H.; Sawayama, Y.; Hashimoto, S.; Nakamura, S. *J. Org. Chem.* **2014**, *79*, 720−735.

(5) A total synthesis of **2** in a racemic form was reported by Mangoni and co-workers in 1972. Mangoni, L.; Adinolfi, M.; Laonigro, G.; Caputo, R. *Tetrahedron* **1972**, *28*, 611−621.

(6) Welch and co-workers reported the synthesis of isomarrubiin (C9-*epi*-marrubiin) through a Cu-catalyzed epoxide ring-opening reaction of the C9-isomer of **3**; however, the complete stereoselection of the epoxide-forming reaction precluded the synthesis of **3**. Welch, S. C.; Rao, A. S. C. P.; Lyon, J. T.; Assercq, J.-M. *J. Am. Chem. Soc.* **1983**, *105*, 252−257.

(7) For recent reviews, see: (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (b) Gibson, S. E.; Stevenazzi, A.

DOI: 10.1021/acs.orglett.6b01602
Org. Lett. 2016, 18, 3430−3433

Angew. Chem., Int. Ed. **2003**, *42*, 1800−1810. (c) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32−42. (d) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022−3037. (e) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, *2005*, 2547−2570. (f) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328−2336. (g) Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, *2010*, 789−811. (h) Kitagaki, S.; Inagaki, F.; Mukai, C. *Chem. Soc. Rev.* **2014**, *43*, 2956−2978. (i) Röse, P.; Hilt, G. *Synthesis* **2016**, *48*, 463−492. (j) Simeonov, S. P.; Nunes, J. P. M.; Guerra, K.; Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2016**, *116*, 5744−5893. (k) Jeong, N. The Pauson−Khand Reaction. In *Comprehensive Organic Synthesis II*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam, 2014; Vol. *5.24*, pp 1106−1178.

(8) For selected recent applications in synthesis of natural products, see: (a) Lv, C.; Yan, X.; Tu, Q.; Di, Y.; Yuan, C.; Fang, X.; Ben-David, Y.; Xia, L.; Gong, J.; Shen, Y.; Yang, Z.; Hao, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 7539−7543. (b) Clark, J. S.; Xu, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 4332−4335. (c) You, L.; Liang, X.-T.; Xu, L.-M.; Wang, Y.-F.; Zhang, J.-J.; Su, Q.; Li, Y.-H.; Zhang, B.; Yang, S.-L.; Chen, J.-H.; Yang, Z. *J. Am. Chem. Soc.* **2015**, *137*, 10120−10123. (d) McKerrall, S. J.; Jørgensen, L.; Kuttruff, C. A.; Ungeheuer, F.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5799−5810. (e) Williams, D. R.; Shah, A. A. *J. Am. Chem. Soc.* **2014**, *136*, 8829−8836. (f) Yang, Y.; Fu, X.; Chen, J.; Zhai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 9825−9828. (g) Liu, Q.; Yue, G.; Wu, N.; Lin, G.; Li, Y.; Quan, J.; Li, C.-c.; Wang, G.; Yang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12072−12076. (h) Mehta, G.; Samineni, R.; Srihari, P. *Tetrahedron Lett.* **2012**, *53*, 829−832. (i) Su, S.; Rodriguez, R. A.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 13922−13925. (j) Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8025−8028.

(9) (a) Yeh, M.-C. P.; Tsao, W.-C.; Ho, J.-S.; Tai, C.-C.; Chiou, D.-Y.; Tu, L.-H. *Organometallics* **2004**, *23*, 792−799. (b) Choi, S. Y.; Lee, S. I.; Park, K. H.; Chung, Y. K. *Synlett* **2007**, *2007*, 1857−1862.

(10) For the use of cycloalkenes in an intramolecular Pauson−Khand (type) reaction to construct all carbon tricyclic systems, see: (a) Carceller, E.; García, M. L.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *Tetrahedron* **1986**, *42*, 1831−1839. (b) Paquette, L. A.; Borrelly, S. *J. Org. Chem.* **1995**, *60*, 6912−6921. (c) Tormo, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4851−4856. (d) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450−9451. (e) Pagenkopf, B. L.; Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse, T. *Synthesis* **2000**, *2000*, 1009−1019. (f) Nüske, H.; Bräse, S.; de Meijere, A. *Synlett* **2000**, *2000*, 1467−1469. (g) Son, S. U.; Park, K. H.; Seo, H.; Chung, Y. K.; Lee, S.-G. *Chem. Commun.* **2001**, 2440−2441. (h) Sturla, S. J.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 3398−3403. (i) Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2007**, *9*, 5625−5628. (j) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684−1687.

(11) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292.

(12) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801−2804.

(13) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854.

(14) Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2001**, *123*, 1703−1708.

(15) For the use of $RuCl_3$, $NaIO_4$, see: Webster, F. X.; Rivas-Enterrios, J.; Silverstein, R. M. *J. Org. Chem.* **1987**, *52*, 689−691.

(16) For the use of OsO_4, NMO/$NaIO_4$, see: Gesinski, M. R.; Brenzovich, W. E., Jr.; Staben, S. T.; Srinilta, D. J.; Toste, F. D. *Tetrahedron Lett.* **2015**, *56*, 3643−3646.

(17) For the use of O_3/aq H_2O_2, NaOH, see: Yates, P.; Burke, P. M. *Can. J. Chem.* **1987**, *65*, 1695−1704.

(18) To the best of our knowledge, this is the first example of activated carbon-mediated decarbonylation of α-ketocarboxylic acids. Since the same reaction occurred when using α-ketocarboxylic acid **11** obtained by ozonolysis of enone **10** with reductive workup (O_3, CH_2Cl_2, −78 °C; Bu_3P), the participation of residual Mn salt could be excluded.

(19) Frontana-Uribe and co-workers reported that a tetracyclic compound having a 4,5,6,7a-tetrahydro-2*H*-furo[2,3-*b*]pyran skeleton was obtained by electrochemical oxidation of the furan moiety of hispanolone in MeOH. Nieto-Mendoza, E.; Guevara-Salazar, J. A.; Ramírez-Apan, M. T.; Frontana-Uribe, B. A.; Cogordan, J. A.; Cárdenas, J. *J. Org. Chem.* **2005**, *70*, 4538−4541.

(20) Internal transacetalization of hydroxybisacetal **16** did not occur upon exposure to TsOH in benzene.

(21) (a) Barbier, C.; Gagnaire, D.; Vottero, P. *Bull. Chem. Soc. Chim. Fr.* **1968**, 2330−2338. (b) Hönel, M.; Mosher, H. S. *J. Org. Chem.* **1985**, *50*, 4386−4388.

(22) C15-isomer of **1** could be isomerized to **1** upon exposure to TsOH in undried EtOH at room temperature.

(23) (a) Cocker, W.; Cross, B. E.; Duff, S. R.; Edward, J. T.; Holley, T. F. *J. Chem. Soc.* **1953**, 2540−2548. (b) Hussein, A. A.; Meyer, M. J. J.; Rodríguez, B. *Magn. Reson. Chem.* **2003**, *41*, 147−151.

DOI: 10.1021/acs.orglett.6b01602
Org. Lett. 2016, 18, 3430−3433