OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

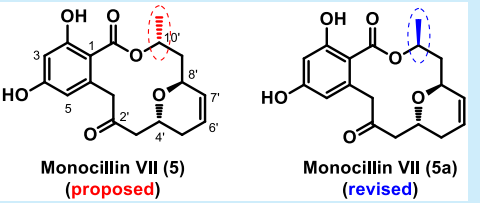
Total Synthesis and Structural Revision of Monocillin VII

N. Arjunreddy Mallampudi,[†] Beduru Srinivas,[†] Jithender G. Reddy,[‡] and Debendra K. Mohapatra*[,†]

[†]Department of Organic Synthesis and Process Chemistry and [‡]Centre for NMR and Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

Supporting Information

ABSTRACT: The first asymmetric total synthesis of macrolactone monocillin VII and its C-10′ epimer was achieved starting from a known chiral pure epoxide in 16 longest linear sequences. The present synthesis highlights the macrolactone formation involving an alkyne−dicobalt carbonyl complex under De Brabander's conditions followed by an unexpected regioselective hydration. The asymmetric total synthesis resulted in the revision of the configuration at C10′ and reassignment of the absolute configuration of the natural product.



The resorcylic acid lactones (RALs) are a class of natural products derived from various organisms and are comprised of a β-resorcylate moiety annulated with 12- or 14-membered macrolactone (Figure 1).[1] Although the structures of most of these compounds are similar to each other, they display varied biological activities such as antimalarial, antifungal, cytotoxic, antiplasmodial, estrogenic, and nematicidal properties, and several members of these RALs acts as potent kinase and ATPase inhibitors.[2] For example, radicicol (**1**) showed potent HSP90 inhibitory activity,[3b−d] while some other RALs exhibited mitogen-activated protein kinase inhibition irreversibly and cytotoxicity against human cells through CDK/GSK-3 inhibition.[3a] As a consequence of their impressive biological activity profiles coupled with structural similarity, considerable efforts were devoted toward their synthetic and pharmacological studies. Recently, Wei and co-workers[4] have isolated eight new resorcylic acid lactones, including monocillin VII (**5**), along with nine known hypothemycin- and radicicol-type RALs from the rice-grown cultures of *Paecilomyces* sp. SC0924. These metabolites have shown antifungal activity against *P. litchii* and *Fusarium verticillioides* and cytotoxicity against MCF-7, A549, and HeLa tumor cell lines. In particular, monocillin VII exhibits antifungal activity against *P. litchii* with an IC_{50} value of 41.0 μM and cytotoxicity against MCF-7, A549, and HeLa tumor cell lines with IC_{50} values of 4.9, 4.1, and 3.9 μM, respectively.[4] The key structural features of monocillin VII (**5**) include the presence of a ketone moiety at the 2′ position, a 4′,8′-*trans* pyran ring with an unsaturation between 6′ and 7′, and a methyl group at the 10′ position. In our group, we developed a synthetic strategy for the synthesis of *trans*-2,6-disubstituted dihydropyrans (DHPs) involving tandem isomerization followed by C−O and C−C bond formation sequence and have utilized the strategy for the synthesis of pyran-containing natural products.[5] In continuation of our interest in the total synthesis of pyran containing natural products and RALs,[6] herein we disclose the total synthesis of macrolactone monocillin VII (**5**) and the revision of the stereochemistry of the natural product.

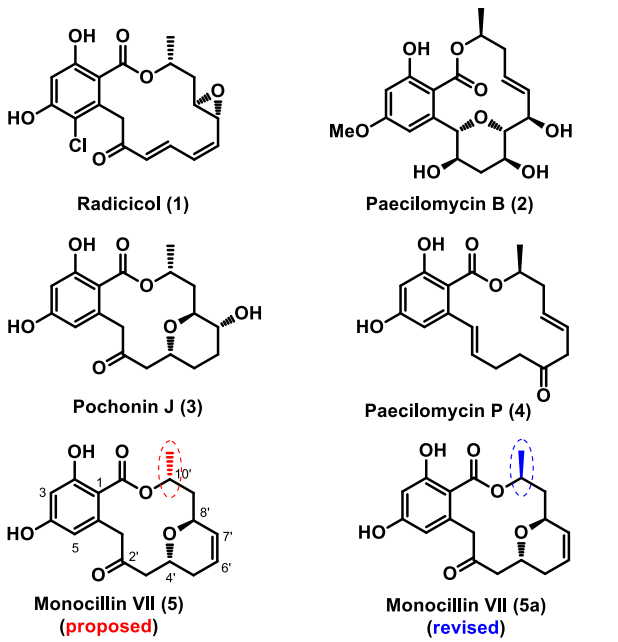


Figure 1. Representative structures of 14-membered resorcylic acid lactones (RALs).

Initially, we planned the synthesis of **5** by transdisposition of the isocouamrin to form the macrolactone. Formation of the key DHP unit was envisaged by the tandem isomerization/C−O/C−C bond-forming protocol[5h] developed by us, while gold(I)-catalyzed 6-*endo-dig* cyclization strategy[7] was anticipated for the synthesis of the isocoumarin fragment.

The key features for the synthesis of monocillin VII are represented in Scheme 1. Initially (path A), we planned that the keto-lactone functionalities could be achieved by the hydrolysis of isocoumarin **8** followed by macrolactonization.

Received: June 17, 2019

DOI: 10.1021/acs.orglett.9b02075
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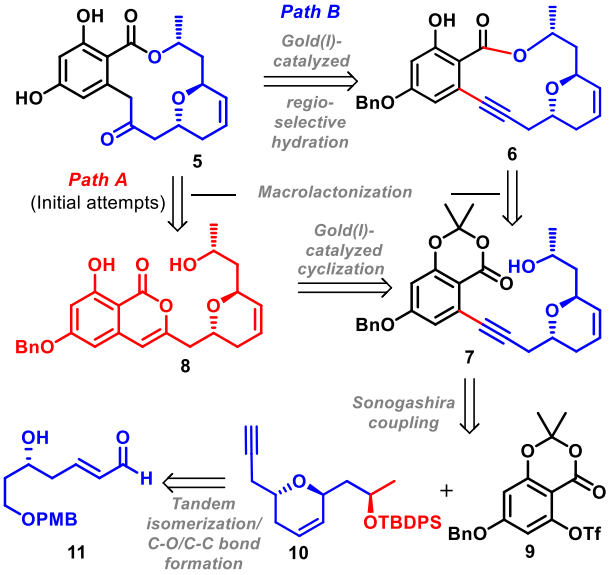
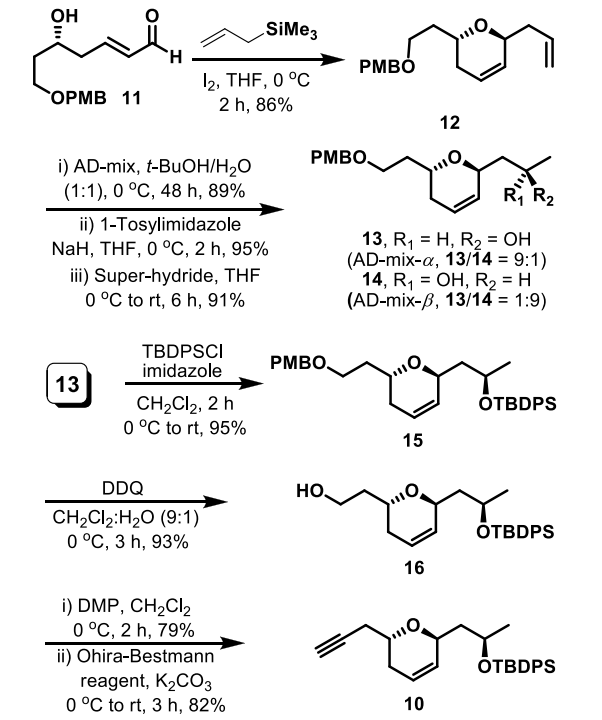
Scheme 1. Retrosynthetic Plan Featuring Gold-Catalyzed 6-*Endo-Dig* Cyclization



The required aryl triflate **9** could be accessed from commercially available 2,4,6-trihydroxybenzoic acid (**17**).

We initiated our study with the synthesis of alkyne fragment **10** required for the key coupling reaction (Scheme 2).

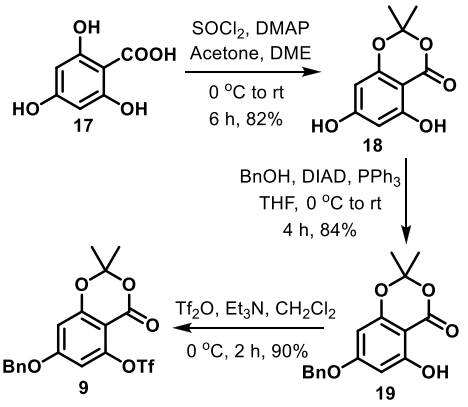
Scheme 2. Synthesis of Alkyne fragment 10



Synthesis of dihydropyran **12** was carried out by following a tandem isomerization/C−O/C−C bond-forming reaction of known aldehyde **11**[5] with 86% yield. The *trans* geometry of the pyran ring was confirmed through 2D-NOE studies. The terminal double bond was subjected to Sharpless asymmetric dihydroxylation in the presence of AD-mix-α[8] to afford (*S*)-diol with its minor diastereomer in 89% combined yield. Reaction of diol with 1-tosylimidazole in the presence of NaH furnished the corresponding epoxide in 95% yield. The epoxide was treated with Super-Hydride in THF to afford the required alcohol **13** along with its minor diastereomer **14** in 91% combined yield, which was separated through silica gel column chromatography. The stereochemistry of both of the hydroxyl groups in compounds **13** and **14** were assigned individually by following the modified Mosher's method (Figures S1 and S2).[9] Esterification of the major alcohol **13** with both (*S*)- and (*R*)-methoxy(trifluoromethyl)phenylacetic acid (MTPA) revealed a positive chemical shift difference [$\Delta\delta = (\delta_S - \delta_R) \times 10^3$] for protons on C10 (Figure S1), while protons on C8 through C1 showed negative chemical shift differences, which is consistent with C-9 bearing an *R*-configuration. The hydroxyl group present in **13** was protected as its TBDPS ether using TBDPSCl and imidazole in CH_2Cl_2 to obtain **15** with 95% yield. The PMB group was oxidatively removed under DDQ conditions[10] to furnish the primary alcohol **16** in 93% yield. The primary alcohol **16** was oxidized under Dess−Martin periodinane conditions to afford the corresponding aldehyde, which was immediately subjected to one carbon homologation using Ohira−Bestmann reagent[11] to afford alkyne **10** in 82% yield.

Synthesis of the aryl triflate **9**, required for the Sonogashira coupling, was synthesized from commercially available 2,4,6-trihydroxybenzoic acid (**17**) (Scheme 3). Reaction of **17** with

Scheme 3. Synthesis of Aryl Triflate 9



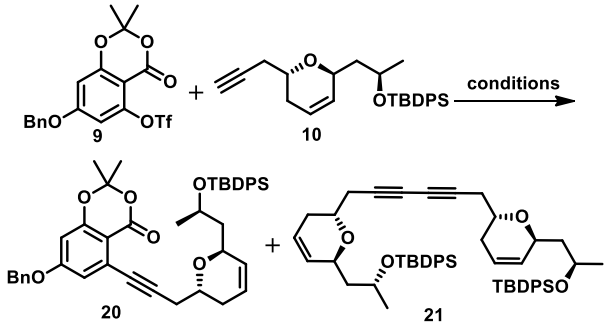
$SOCl_2$, DMAP, and acetone gave the acetonide **18** in 82% yield. The hydroxyl group in **18** was selectively protected as its benzyl ether under Mitsunobu conditions[12] to obtain **19** in 84% yield. Finally, the free hydroxyl group in **19** was converted to triflate **9** using Tf_2O and Et_3N in CH_2Cl_2 with 90% yield.[7]

Having both the coupling partners in hand, we planned to perform the key Sonogashira coupling reaction. Initial attempts under standard Sonogashira conditions[13] either failed or produced a lower amount (<10%) of required product **20**, and the homocoupled product **21** was obtained as the major product. To circumvent this problem, we optimized the coupling reaction conditions using various palladium catalysts by changing the ligands and bases (Table 1). Finally, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, CataCxium A, and K_2CO_3 conditions using acetonitrile as the solvent at 60 °C furnished the heterocoupled product **20** in 76% yield (Table 1).

After having the coupled product, the TBDPS group was deprotected with NH_4F in MeOH at 50 °C to afford the alkyne **7** in 85% yield. Compound **7** was subjected to PPh_3AuCl and $AgSbF_6$ under 1,4-dioxane conditions to furnish

DOI: 10.1021/acs.orglett.9b02075
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of the Sonogashira Coupling of Aryltriflate 9 and Alkyne 10



entry[a]	conditions	yield (%)[b]
1	$(PPh_3)_2PdCl_2$, Et_3N, CuI, DMF, rt	10
2	$(PPh_3)_4Pd$, Et_3N, CuI, DMF, rt	5
3	$Pd(dba)_2$, Et_3N, CuI, DMF, rt	0
4	$(PPh_3)_2PdCl_2$, Et_3N, CuI, CH_3CN, rt	15
5	$Pd(dppf)_2{\cdot}CH_2Cl_2$, K_2CO_3, DMF, rt	10
6	$Pd(dppf)_2{\cdot}CH_2Cl_2$, K_2CO_3, CH_3CN, rt	20
7	**$Pd(dppf)_2{\cdot}CH_2Cl_2$, K_2CO_3 CataXCium A, CH_3CN, 60 °C**	**76**[c]
8	$Pd(dppf)_2{\cdot}CH_2Cl_2$, K_2CO_3, Xantphos, CH_3CN, 60 °C	30[c]
9	$Pd(dppf)_2{\cdot}CH_2Cl_2$, K_2CO_3, nBu$_3$P, CH_3CN, 60 °C	5[c]
10	$Pd(dppf)_2{\cdot}CH_2Cl_2$, Cs_2CO_3, CataXCium A, CH_3CN, 60 °C	35[c]

[a]The reactions were performed with **10** (1 mmol), **9** (1.2 mmol), catalysts (5 mol %), and base (1.5 mmol) in solvent (2 mL) at specified temperatures under argon atmosphere. [b]Yield of isolated product after column chromatography. [c]5 mol % of phosphine ligand. In all cases, formation of homocoupled product **21** was also observed.

the isocoumarin derivative **8** in 88% yield.[7] To obtain the keto acid derivative, standard ester hydrolysis conditions were attempted (LiOH or KOH in THF/H_2O).[14] However, all attempts to hydrolyze the isocoumarin under different reaction conditions were unsuccessful and led to an intractable mixture of products. Disappointed yet undaunted by the failure to afford the keto acid intermediate, we proceeded to revise our synthetic protocol (path B). The pivotal macrolactone formation was envisaged by an intramolecular macrolactonization keeping an alkyne group in the carbon chain in the 14-membered ring. Our hypothesis for this route stems from the observation that the regioselectivity in hydration of alkynes can be achieved by neighboring group assistance,[15] so that the keto group present at 2′ could be accessed from the alkyne via intramolecular oxygen-assisted regioselective hydration reaction.

Accordingly, macrolactonization formation of seco-acid derivative **7** was performed under De Brabander's conditions[16] (NaH, THF, 0 °C) to afford the lactone **6**, albeit in poor yield (15%), with the recovery of starting material (~76%) and nonreproducible results. Most likely, conformational constraints on the backbone imposed by the linear structural nature of the alkyne unit restrict the cyclization leading to very poor yield. It is well known that reaction of dicobalt octacarbonyl with alkynes can lead to stable complexes wherein the geometry of the cobalt-complexed alkyne is distorted to approximately 140°.[17] To resolve the problem of macrolactonization with very poor yield, it was envisioned that Co-complexed intermediate **23** may deliver compound **6** with good yield.[18] Accordingly, compound **7** was treated with $Co_2(CO)_8$ in CH_2Cl_2 at 0 °C to afford the Co complex **23** in almost quantitative yield (Scheme 4). Most notably the presence of cobalt complex was evident in the NMR spectra of the sample while the mass spectrum established the presence of cobalt complex formation in compound **23**. As this complex was not very stable, we immediately used it in the macrocyclization reaction. Consistent with the above hypothesis, when compound **23** was treated with NaH in a mixture of THF and DMF (9:1) at 50 °C, the only isolable product of the reaction was compound **6** in 52% yield accompanied by the recovery of 35% of the alcohol **7**.[16] Now the stage was set to execute the vital gold-catalyzed regioselective hydration reaction[15] for the introduction of ketone. Delightfully, treatment of lactone **6** with PPh_3AuCl, AgOTf, and H_2O in 1,4-dioxane furnished the hydration product exclusively at the nonbenzylic position of the alkyne with good yield. The observed high regioselectivity is presumably attributed to the intramolecular assistance of ester group for the hydration reaction. To the best of our knowledge, such a regioselective gold-catalyzed hydration on alkynyl lactones has not been reported in the syntheses of RALs. With keto lactone **24** in hand, we proceeded to the completion of the synthesis of monocillin VII. Debenzylation of keto lactone **24** was carried out with excess $TiCl_4$ in CH_2Cl_2 at 0 °C to afford monocillin VII (**5**) with 89% yield.[19]

However, the ^{1}H NMR and ^{13}C NMR data for the synthetic compound **5** showed deviations from the data reported for the natural product,[4] strongly suggesting a structural misassignment during the isolation of the natural product. Moreover, the specific rotation for the synthetic compound **5** {($[\alpha]_D^{20}$ −7.3 (*c* 0.26, MeOH)} showed the same sign but varied in magnitude with that of natural product {lit. ($[\alpha]_D^{20}$ −31.2 (*c* 0.25, MeOH)}. As some other members of this series isolated from *Paecilomyces* sp. SC0924 having the *S*-configured methyl group at the 10′ position,[4] we thought that the natural product may be the diastereomer of the proposed structure. Thus, we undertook the total synthesis of 10′(*S*)-isomer (**5a**) of the proposed structure. Accordingly, (4′*R*,8′*S*,10′*S*)-monocillin VII (**5a**) was synthesized from compound **14** by a synthetic route similar to that described for **5** (Scheme 5), where alcohol **14** was prepared from compound **12** using AD-mix-*β*. Delightfully, the spectral data (^{1}H and ^{13}C NMR) of **5a** were in good agreement with those reported for the natural product (see the comparison of the NMR data of natural monocillin VII, synthetic **5** and **5a** in Table S1). The specific rotation for synthetic **5a** ($[\alpha]_D^{20}$ −19.7 (*c* 0.21, MeOH) also showed the same sign but deviated in magnitude {(lit. $[\alpha]_D^{20}$ −31.2 (*c* 0.25, MeOH)}.

Extensive NMR studies on synthetic compounds **5** and **5a** were carried out in C_5D_5N using 1D (^{1}H and ^{13}C) and 2D (DQF-COSY, TOCSY, NOESY, HSQC and HMBC) NMR experiments. In comparison to the reported natural product, the ^{1}H and ^{13}C NMR spectral data of compound **5** showed major discrepancies, whereas the data from compound **5a** are in full agreement (Table S1). However, the presence of medium-range NOE correlations between H-1′*β*/H-4′, H-3′*β*/H-4′, H-9′*β*/H-4′, and H-9′*α*/H-8′ in both compound **5** and **5a** suggested that the configurations at H-4′ and H-8′ are in *α*- and *β*-orientations, respectively. The characteristic difference in compound **5** is the presence of NOE between H-8′/CH_3-11′ supporting an "*R*" configuration, whereas in compound **5a** it is between H-8′/H-10′ supporting an "*S*" configuration at C10′. This is further confirmed by the scalar coupling (*J*)

DOI: 10.1021/acs.orglett.9b02075
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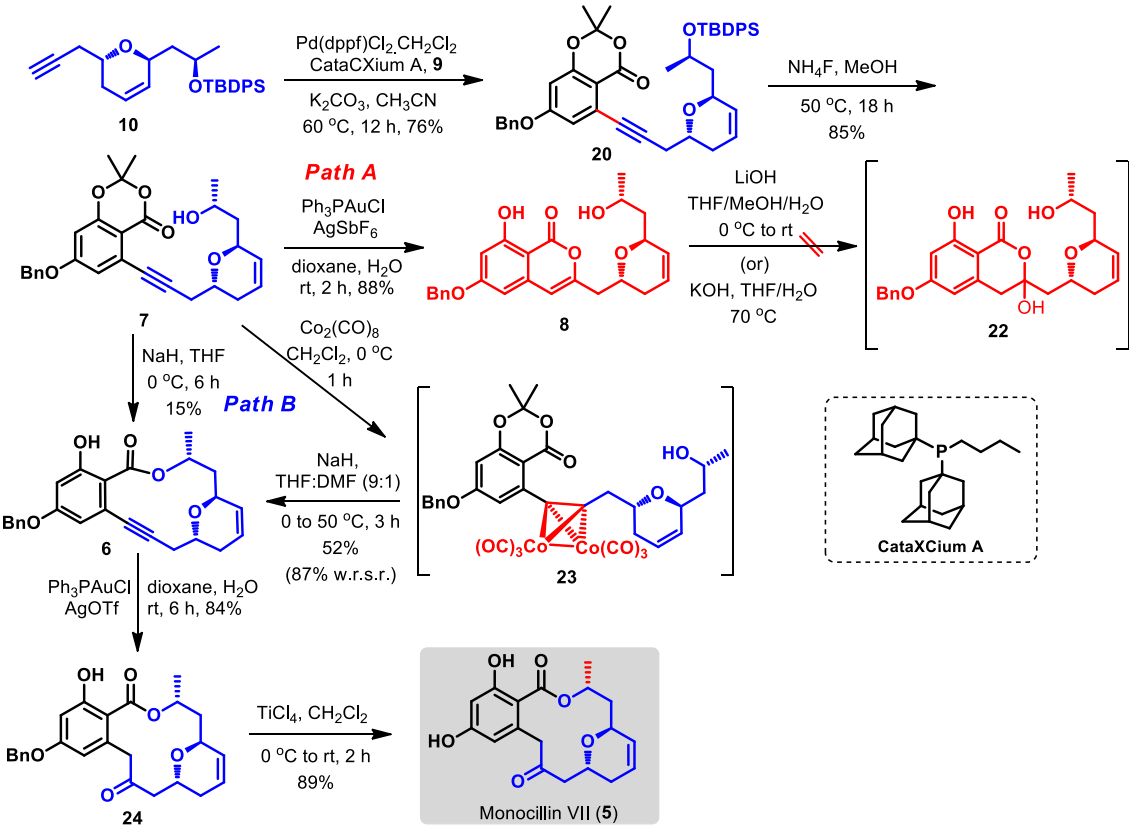
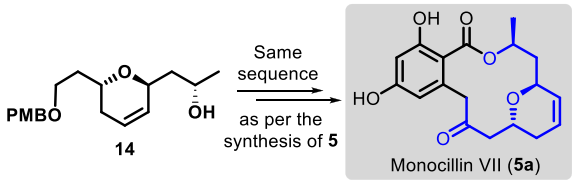
Scheme 4. Synthesis of Monocillin VII (5)



Scheme 5. Synthesis of Monocillin VII (5a)



between H-9′β/H-10′ which is 2.0 and 10.4 Hz in compound **5** and **5a** (10.8 Hz as observed in natural product), respectively. Overall, chemical shifts and characteristic scalar couplings of compound **5a** are in full agreement with that of natural product (Table S1), whereas the stereocenter at C10′ carbon shows an "*S*" configuration in compound **5a**. Complete NMR studies of both compounds adequately supported that the compound **5** has a (4′*R*,8′*S*,10′*R*) configuration (Figure S4) and compound **5a** has a (4′*R*,8′*S*,10′*S*)-configuration (Figure S6). Given that, the complete NMR spectral data were reassigned the absolute stereochemistry of the natural product to compound **5a** with a 4′*R*,8′*S*,10′*S* configuration.

In conclusion, an efficient convergent synthetic route has been developed for an asymmetric first total synthesis of monocillin VII in 16 longest linear sequences starting from a known chiral pure epoxide which was obtained by Jacobsen's hydrolytic kinetic resolution. The 2,6-*trans*-disubstituted tetrahydropyran ring present in monocillin VII was achieved by using the tandem isomerization followed by a C−O/C−C bond-forming reaction developed by our group. The work reported herein highlights the construction of the macrolactone ring system following a convergent union of the elaborated subunits through modified Sonogashira coupling and the dicobalt carbonyl complex of alkyne to execute smooth macrocyclization under De Brabander's conditions followed by unexpected regioselective hydration and to introduce the functionality relevant to the synthesis of RALs and related natural products. The total synthesis of monocillin VII and its C10′-epimer followed by comparison of their ^{1}H and ^{13}C NMR data with those of the natural product led us to correct the previously proposed structure to that of (4′*R*,8′*S*,10′*S*)-monocillin VII (**5a**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02075.

Detailed experimental procedures and spectral data (^{1}H, ^{13}C and 2D-NMR) for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mohapatra@iict.res.in.

ORCID

Debendra K. Mohapatra: 0000-0002-9515-826X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support received from Department of Science and Technology-Science and Engineering Research Board (DST-SERB), New Delhi,

DOI: 10.1021/acs.orglett.9b02075
Org. Lett. XXXX, XXX, XXX−XXX

India, through Grant No. EMR/2017/002298 (GAP-0761); Manuscript communication number IICT/Pubs/2019/256. N.A.M and B.S thank CSIR and UGC, New Delhi, India, for financial assistance in the form of fellowships.

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DOI: 10.1021/acs.orglett.9b02075
Org. Lett. XXXX, XXX, XXX−XXX