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Application of Pd-Catalyzed C−H Alkylation Reaction in Total Syntheses of Twelve Amicoumacin-Type Natural Products

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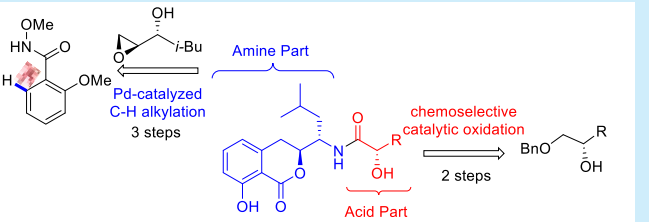
ABSTRACT: Enantioselective total syntheses of 12 amicoumacin-type natural products are accomplished with a palladium(II)-catalyzed C−H alkylation as the key step to furnish the 3,4-dihydroisocoumarin scaffold. The target chemicals are assembled in a convergent protocol by merging 3,4-dihydroisocoumarin derived amine part with categories of acid segments that are efficiently prepared by chemoselective catalytic oxidation of chiral 1,2-dihydroxyethylfuran-2(5H)-ones. Afterward, the cytotoxicity of amicoumacins on five cancer cell lines and one normal cell line is investigated.

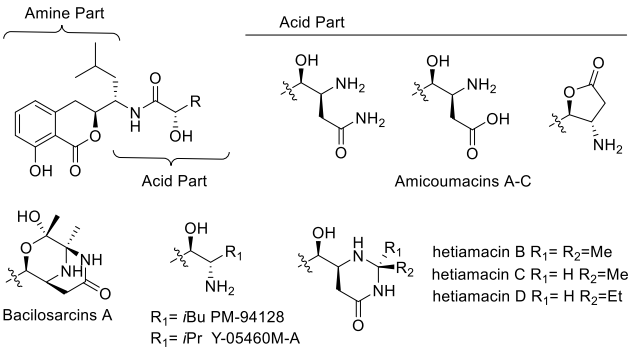


Isocoumarins and 3,4-dihydroisocoumarins (DHIC; 1H-2-benzopyran-1-one) are ubiquitous scaffolds occurring in categories of natural products.[1] Among them, great attentions are particularly attached to amicoumacins and amicoumacin-related antibiotics[2] as they have been found to possess attracting bioactivities ranging from antibacterial to antitumor.[3] For example, in a recent biochemical study, it has been disclosed that amicoumacin A belongs to a new class of inhibitors that can affect the translation elongation in ribosomes.[4] The molecular structures of amicoumacins can be divided into two parts: the 3,4-dihydroisocoumarin moiety and different acyl hydroxy amino acid chains (Scheme 1). Moreover, the classification of the family of amicoumacin-type antibiotics was also based on the variation in the amino acid.

Because of their favorable bioactivities as well as the unique molecular architectures, a wide spectrum of synthetic methods toward amicoumacin-type natural products has been developed. For the constant amine part (containing DHIC), most of the published synthetic approaches were based on the coupling of aryl Grignard/lithium reagents with commercially available L-leucine/D-ribose derivatives[5,6] or epoxides prepared by Sharpless oxidation.[7] In addition, Diels−Alder- and Heck-based approaches[8,9] for the synthesis of the amine part were also successfully conducted. As for the acid part, the sources of chiral starting material include amino acid/carbohydrate derivatives,[10,11] benzyl sorbate,[12] and arenetricarbonylchromium,[13] besides, the chiral inductors like (R)-valinol[14] and indane derivatives[15] were also used for the construction of the acid part. However, these protocols for the syntheses of amicoumacins always need multiple steps and have critical problems concerning the chemical yield.

In order to increase the efficiency of synthesizing these compounds and in continuation of our interest in Pd-catalyzed C−H alkylation with epoxys, herein, we report an efficient approach to construct these amicoumacin-type skeletons, which need only three steps to give access to the 3,4-dihydroisocoumarin moiety (amine part) by Pd-catalyzed C−H alkylation and two steps to render the acid segment by using known chiral furanone as a starting material. The retrosynthetic analysis of amicoumacin-type skeleton **1** is shown in Scheme 2. Amicoumacins and closely related compounds

Scheme 1. Amicoumacins A−C and Some Structural Closely-Related Natural Products



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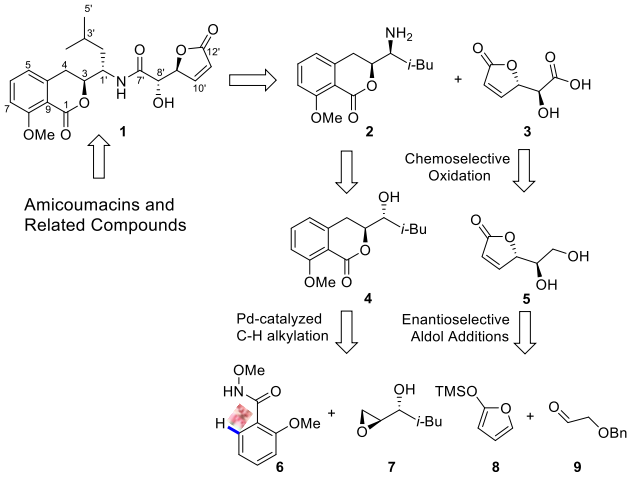
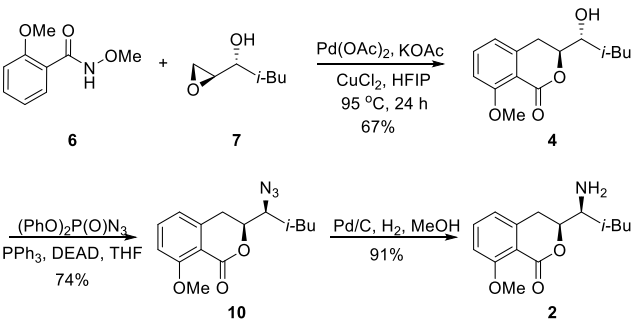
Scheme 2. Retrosynthetic Analysis of Amicoumacin-Type Skeletons



should be obtainable via decoration of compound **1**, which is proposed to be assembled via peptide coupling of the amine part **2** with the acid part **3**. The amine part **2** could be traced back to corresponding alcohol **4** with inversion of C3 configuration. For the preparation of **4**, our previously employed method in the total synthesis of (−)-berkelic acid,[16] namely, Pd(II)-catalyzed C−H alkylation of *N*-methoxybenzamide with epoxides should be appropriate to construct the 3,4-dihydroisocoumarin motif in **4**. On the other hand, the acid part **3** would be derived from chemoselective oxidation of 1,2-diol **5**, which is considered to be readily accessible by enantioselective aldol addition developed by Evans in 1998.[17]

With the above retrosynthetic analysis in mind, our syntheses of these amicoumacin-type natural products began with the synthesis of the 3,4-dihydroisocoumarin motif in the amine part **2** (see Scheme 3). Since the sequential reports of

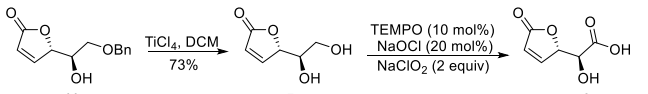
Scheme 3. Preparation of the 3,4-Dihydroisocoumarin Moiety 2



Pd-catalyzed C−H alkylation reactions of arylpyridines and benzoic acids with epoxides in 2015,[18] these types of reactions have been fully developed[19] and used as a labor-saving alternative to construct isochroman-based natural products.[16,20] Recently, we found that *N*-methoxyamide as a stronger coordinating directing group, compared to carbonyl, gave higher yields of 3,4-dihydroisocoumarins under slightly basic conditions, especially for the substrates incorporating multiple oxygen-containing functional groups.[19d] Thus, we applied this optimized reaction condition to *N*,2-dimethoxybenzamide **6** and epoxy alcohol **7** to render the 3,4-dihydroisocoumarin motif. Notably, in this process, free *β*-hydroxyl group was tolerated, affording compound **4** in 67% yield. Then, transformation of the alcohol into azido with inversion of C-3 configuration gave compound **10** in 74% yield, which was reduced under Pd/C promoted hydrogenation to render amino **2** in an overall yield of 45% from **6**. Note that the free amino lactone **2** is not stable for storage,[21] so it was used immediately or stored as its hydrochloride salt.

The preparation of acid segment **3** commenced with the debenzylation of **11**, which was readily produced in high yield (>90%) by enantioselective aldol addition developed by Evans et al. After obtaining alcohol **5** from **11**, various one-pot oxidation methods were investigated (Scheme 4), and treating

Scheme 4. Preparation of the Acid Segment 3



Entry	Solvent	Buffer	Time(h)	Yield(%)[a,c]
1. Baskaran's condition	Acetone	5% aq.$NaHCO_3$ buffer (pH 8.3)	2	trace
2. Massanet's condition	Acetonitrile	phosphate buffer (pH 6.5)	1-48	trace
3. Shibuya's condition	Toluene	phosphate buffer (pH 6.8)	1-24	trace
4	Toluene:EA=3:1	phosphate buffer (pH 6.8)	12	48(34)[b]
5	ethyl acetate	phosphate buffer (pH 6.8)	12	trace
6	Toluene:EA=3:1	phosphate buffer (pH 6.5)	12	65(21)[b]

[a]Isolated yields. [b]Yield of the oxidative cleavage product. [c]Reaction temperature: 25 °C.

1,2-diol **5** under Baskaran's[22] (1 equiv TEMPO/2 equiv NaClO), Massanet's,[23] and Shibuya's condition[24] (cat. TEMPO/cat. $NaClO/NaClO_2$) all gave only trace amounts of the desired acid **3**. In view of the fact that the key for the successful oxidation of 1,2-diols to corresponding *α*-hydroxy acids is the use of a two-phase condition, which is consisted of hydrophobic solvent and water to suppress the concomitant oxidative cleavage; however, water-soluble 1,2-diols did not produce the desired product under these conditions.[24] In order to make the water-soluble substrate **5** enter to the organic phase to participate in the oxidate reaction, higher water solubility solvent ethyl acetate was added in toluene; to our delight, the yield of *α*-hydroxy acids **3** increased to 48%, accompanied by 34% yield of the oxidative cleavage product (see the Supporting Information). However, using ethyl acetate alone gave only trace amounts of acid **3**, which indicated that the solvent played a crucial role in this type of reaction (entry **5**). Finally, when pH was adjusted from 6.8 to 6.5, the desired acid **3** was obtained in 65% yield with the yield of oxidative cleavage byproduct decreased to 21% (entry **6**).

Having successfully prepared the amine part **2** and acid part **3**, we proceeded to the final stage of the syntheses of compounds **12**−**21** (Scheme 5). Condensation of the acid with the amine in the presence of EDCI gave the key intermediate **1** in 74% yield. Treatment of **1** with BBr_3 in the presence of anisole afforded AI-77-F (**12**), hydrogenolysis of which resulted in the quantitative formation of bacillcoumacin D (**13**). On the other hand, the key intermediate **1** reacted with sodium azide in aqueous acetic acid gave the conjugate adduct product **14** as a 6:1 mixture of its epimer at the azidebearing stereogenic center in 40% yield (86% brsm). Compound **14** was then reduced to **15** by catalytic hydrogenation and followed by direct acylation with the corresponding acyl chlorides in the presence of Et_3N at −10 °C to give

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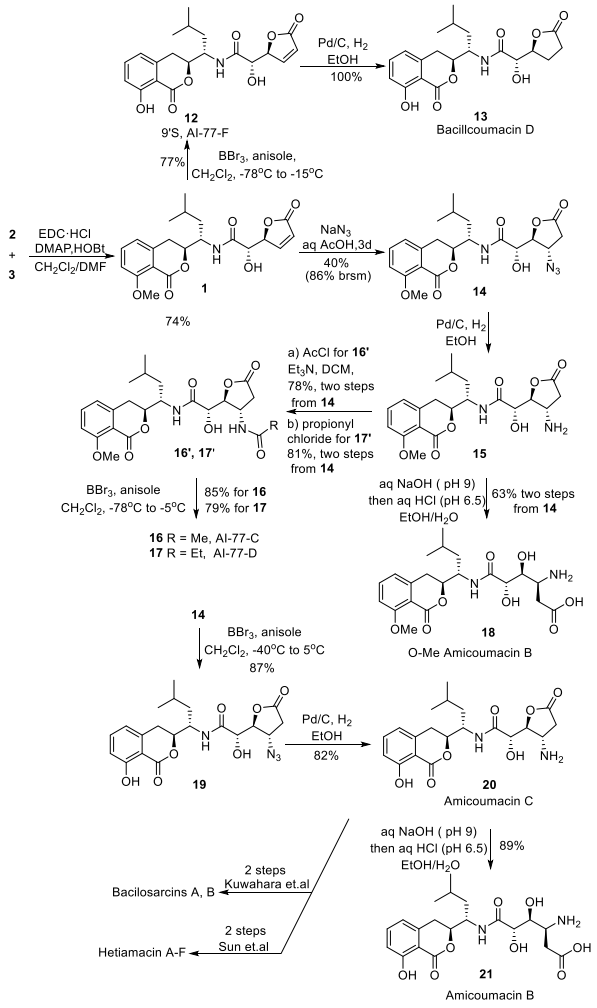
Scheme 5. Syntheses of Amicoumacins and Related Natural Compounds



monoacetate product **16′** and monopropionate product **17′**. Subsequently, unmasking of the methyl protected phenolic hydroxy group provided AI-77-C (**16**) and AI-77-D (**17**) in yields of 85% and 79%, respectively. Compound **15** was also converted to O-Me amicoumacin B (**18**) by opening the γ-lactone ring at pH 9.0. As for the syntheses of amicoumacins, removal of the methyl protecting group of **14** and the subsequent hydrogenation were well-orchestrated. Amicoumacin C (**20**) could easily undergo interconversions upon simple chemical treatments to obtain amicoumacins A and B.[25] In addition, the conversion of amicoumacin C into hetiamacins A−F and bacilosarcins A and B have been respectively reported by the Sun group[26] and the Kuwahara group.[12]

In light of the structural similarity between AI-77-F (**12**) and AI-77-H (**25**) (9′ epimer), we next turned to synthesize AI-77-H by following the synthetic sequence used for **12**; uneventfully, AI-77-H (**25**) was obtained in 36% overall yield from known 1,2-diol **22**.[27] Bacillcoumacin G (**30**), which was isolated as a special metabolite bearing a γ-lactam,[28] was also synthesized by coupling of the amine **2** with the acid segment **28**, followed by BBr_3-promoted demethylation. The acid segment **28** was prepared in two steps from the known 5-thioxopyrrolidin-2-one **26** via the Wittig reaction with $Ph_3P{=}CHCO_2Bn$ and the subsequent $AlCl_3$-promoted debenzylation. At last, the total syntheses of PM-94128 (**31**), Y-05460M-A (**32**), and bacillcoumacin A (**34**) were also achieved by coupling of Kuwahara's acid[10d] or 2-(benzyloxy)acetic acid **33′** with our amine part **2**.

Although the cytotoxicity of these natural products has been preliminarily evaluated by the isolated team,[28,3b] only a few cancer cell lines were tested and no normal cell line was selected. Herein, these synthesized amicoumacin-type natural products were assessed for their cytotoxicity against five other human tumor cell lines, including RKO (colon cancer), BGC-823, SCG-7901, MCG-803, NCI-N87 (gastric cancer), and one normal cell line (WI-38) by the MTT method. As shown in Table 1, only compounds PM-94128 (**31**) and Y-05460M-A (**32**), which bear an isobutyl or isopropyl group in the C10′ position, exhibited broad-spectrum cytotoxicity against tested cancer cell lines and are superior to the positive drug 5-fluorouracil with IC_{50} ranging from 0.06 to 13.82 μM. Unfortunately, they also possessed considerable toxicity on the non-cancer cell line (WI-38, IC_{50} = 6.99, 7.70 μM respectively). Compounds **18** and **21**, which can be regarded as derivatives of **31** ($R_1{=}CH_2COOH$; see Scheme 6), showed no significant cytotoxicity in the same assay, indicating that the R_1 group of amicoumacins plays a critical role in cytotoxicity. This was further supported by the comparison of IC_{50} values between PM-94128 (**31**) and Y-05460M-A (**32**). As for the analogues bearing a γ-lactone (**12**, **13**, **16**, **17**, **20**, **25**) or γ-lactam ring (**30**), only AI-77-H (**25**) showed weak inhibitory activity against NCI-N87 with an IC_{50} value of 35.32 μM, which indicated that unsaturated lactone ring and stereogenic center C-9′ directly affected the inhibitory effects.

In summary, a practical and enantioselective synthetic route to amicoumacins has been developed. The skeleton of amicoumacins was assembled in a convergent protocol by merging the 3,4-dihydroisocoumarin-derived amine part with categories of acid segments. The amine part, which is common in all members of the amicoumacin-type natural products, was prepared by Pd(II)-catalyzed C−H alkylation of *N*-methoxybenzamide **6** with epoxy alcohol **7**. On the other hand, the acid segments were efficiently prepared by chemoselective catalytic oxidation of chiral 1,2-dihydroxyethylfuran-2(5H)-

Table 1. Cytotoxicity of Synthesized Natural Products[a] (IC_{50}, μM)

	Cytotoxicity, IC_{50} (μM)					
compound	RKO	BGC-823	SCG-7901	MGC-803	NCI-N87	WI-38
AI77-H (**25**)	>150	>150	95.64 ± 2.31	>150	35.32 ± 1.80	>150
PM-94128 (**31**)	0.06 ± 0.004	5.20 ± 0.31	0.10 ± 0.01	0.37 ± 0.01	0.41 ± 0.03	6.99 ± 0.41
Y-05460M-A (**32**)	0.32 ± 0.02	13.82 ± 1.10	0.15 ± 0.03	0.76 ± 0.05	1.03 ± 0.01	7.70 ± 0.33
5-FU[b]	20.30 ± 1.34	40.54 ± 1.65	10.58 ± 1.13	9.37 ± 1.10	23.62 ± 2.04	>150

[a]All values are presented as mean ± SD (n = 3). The cytotoxicity was evaluated after 72 h of treatment before performing the MTT assay. The IC_{50} values were analyzed using IBM SPSS Statistics software. [b]5-FU = 5-fluorouracil.

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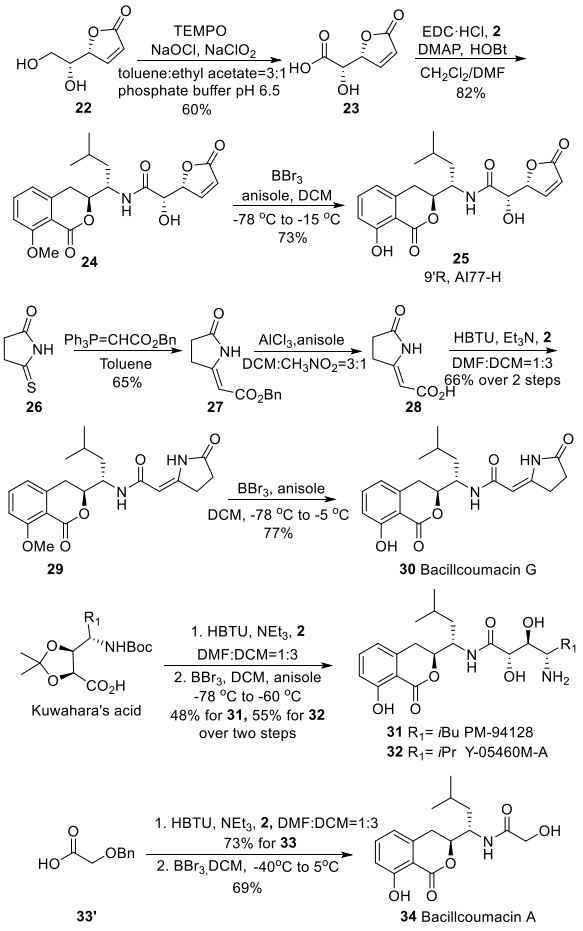
Scheme 6. Syntheses of Five Related Natural Compounds



ones. Finally, this divergent strategy allows to provide enough materials for our biological activity studies. As a result, PM-94128, Y-05460M-A, and AI-77-H were revealed to possess cytotoxic effect on human cancer cell lines, which offers a chance to perform more in-depth biological investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02576.

Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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