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Iromycins: A New Family of Pyridone Metabolites from *Streptomyces* sp. II. Convergent Total Synthesis

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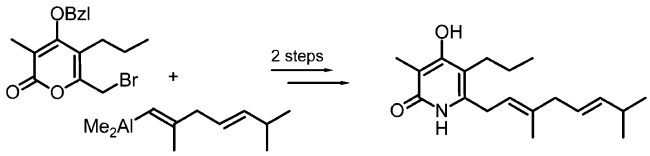
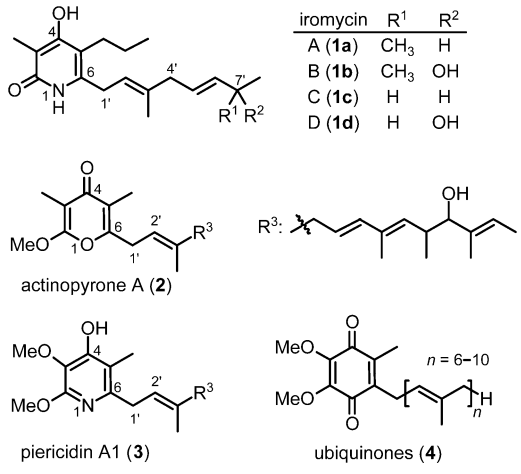
Received February 16, 2007



The total synthesis of iromycin A (**1a**), a microbial metabolite combining a novel structure with an interesting biological activity as a NO synthase inhibitor, was accomplished using a flexible and highly convergent approach. Thus, the ring fragment was prepared as 6-bromomethylpyrone **27** by acylation of the respective β-ketoester **13** and subsequent lactonization of the thus-obtained β,δ-diketoester **11**, followed by bromination of the 6-methyl group. In addition, the unsaturated side chain was efficiently prepared as terminal alkyne **34** which was then carboaluminated to furnish the alkenyldimethylalane **35**. The assembly of these two fragments was thoroughly studied using nickel, palladium, and copper catalysts yet only succeeded in the absence of any transition metal after formation of the respective lithium alkenyltrialkylalanate. Treatment of the coupled product **41** with liquid ammonia then completed the total synthesis which furnished an 18% overall yield over the nine steps of the longest linear sequence.

Introduction

The iromycins (**1**) are a group of microbial polyketide-derived metabolites, recently isolated in yields of up to 18 mg/L from *Streptomyces* sp.[1] Regarding their structure, they are characterized by a fully substituted α-pyridone ring carrying an *n*-propyl chain at C-5 and a branched, unsaturated eight-membered side chain at C-6. Thus, they represent a new family of natural products since they noticeably differ from other pyridone compounds such as tenellin,[2a] the antifungal antibiotic ilicicolin H,[2b] the protein tyrosine kinase inhibitor pyridovericin,[2c] and kirromycin,[2d] an inhibitor of the elongation factor TU. These metabolites also possess long unsaturated side chains, yet they are placed at C-3 of the heterocycle and contain a carbonyl moiety at C-1′ as opposed to the methylene group in the iromycins. Moreover, there are natural products with a similar side chain but a different type of heterocyclic moiety such as the ichthyotoxic kalkipyrone,[3a] the actinopyrones[3b] (e.g., **2**) with



a vasodilating activity, and the piericidins[3c] (e.g., **3**), which exhibit a strong inhibition of the mitochondrial electron transfer chain protein NADH-ubiquinone reductase as they presumably mimic the ubiquinones (**4**) themselves. The iromycins (**1**) also bear a highly interesting biological activity since they selectively

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10.1021/jo070327j CCC: $37.00
Published on Web 06/12/2007

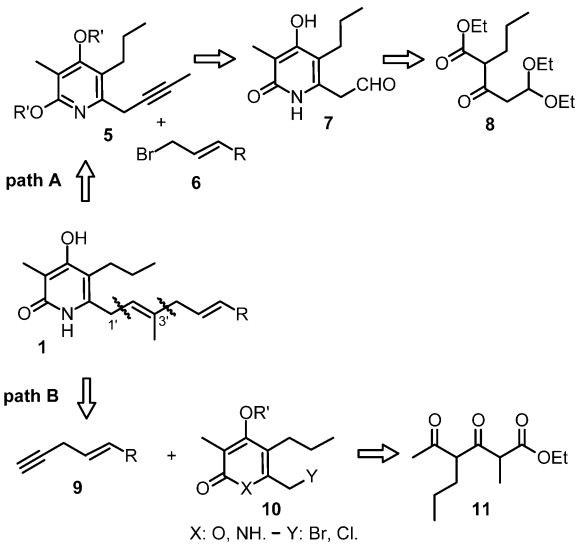
inhibit the nitric oxide synthase (NOS) and thus the release of this crucial second messenger molecule.[1] In particular, they are the first natural products showing a differentiating influence on the isoforms of NOS and thus might become valuable biochemical tools. Additionally, an apparent structure−activity relationship was observed since iromycin A (**1a**) with its terminal isopropyl group is a stronger inhibitor than the hydroxylated derivative B (**1b**) or C (**1c**) that possesses just a terminal ethyl group.[1a] This combination of structural novelty and promising biological activity makes the total synthesis of the iromycines and *their* non-natural derivatives an attractive aim. Herein, we report on our work toward a general and efficient synthesis of this family of natural products.

Results and Discussion

Synthetic Considerations. Due to the interest in the synthesis of a number of derivatives, a convergent and flexible approach involving the coupling of the side chain and the ring fragment at a later stage of the sequence was anticipated as this would allow for a systematic alteration of each half of the molecule. On a similar basis, a few syntheses of piericidins[4] and derivatives thereof have been performed, and very recently the synthesis of verticipyrone was accomplished.[5] Thus, Boger et al.[4a] disconnected compound **3** at the C-1′—C-2′ bond and performed a Stille-type coupling of the respective 6-bromomethylpyridine with the side chain as alkenylstannane, which proceeded in good yield yet required 50 mol % of palladium catalyst. On the contrary, the C-6—C-1′ bond was formed in Stille-type reactions of stannylated pyridine or benzene derivatives with an allylic carbonate or halide in syntheses of piericidin analogues by Keaton and Phillips[4b] or Ono, Akita et al.,[4c] respectively, but these transformations afforded mixtures of the desired (*E*)- and the undesired (*Z*)-isomers. Finally, Rapoport et al.[4d] prepared piericidin analogues by reaction of a lithiated pyridine derivative with various prenyl bromides.

For the synthesis of the iromycins two different strategies were envisaged, both of them relying on a stereo- and regioselective metalation of an alkyne moiety (Scheme 1). Thus, a disassembly of the molecule at the C-3′—C-4′ bond would lead to ring fragment **5** which would be coupled with allyl bromides **6** via hydrozirconation[6] of the triple bond with the Schwartz reagent $Cp_2Zr(H)Cl$ and a subsequent transition-metal-catalyzed cross-coupling reaction (path A). The pyridine **5** in turn would be prepared from the pyridone **7** by a carbon homologation of the aldehyde using the Corey−Fuchs protocol.[7] Since this approach promised a particular rapid variation of the terminal group R in the iromycins (**1**), it was initially tested yet was abandoned due to problems in the preparation of aldehyde **7** from β-ketoester **8** (see Supporting Information for details).

SCHEME 1. Retrosynthetic Analysis of the Iromycins (1)



A second path comprised a scission of the C-1′—C-2′ bond (path B), and the C—C coupling was intended to be achieved by carboalumination[8a] of enynes **9** with $AlMe_3$ followed by cross-coupling of the thus obtained alkenyldimethylalanes with a 6-halomethylheterocycle **10**. This procedure has been performed under Ni-catalysis by Lipshutz et al.[8b] in their efficient synthesis of the ubiquinones (**4**). The ring fragment **10** would now stem from cyclization of β,δ-diketoester **11** to form a pyrone[9] and subsequent transformations including functionalization of the methyl substituent at C-6 of the heterocycle.

Preparation of Ring and Side Chain Fragments. For the synthesis of iromycin A (**1a**) along path B a number of different ring fragments **10** were prepared since the cross-coupling with alkenylalanes later on proved to be quite difficult. At first, the synthesis of the required β,δ-diketo acid **11** was performed using the methodology of Weiler et al.[10] for the generation and transformation of the dianions of β-ketoesters (Scheme 2). The starting material **12** was lithiated and then alkylated to give ethyl heptanoate **13** in 56% yield using *n*PrI while *n*PrBr furnished the desired product in only 25% yield. Acylations in the γ-position of β-ketoesters have been performed using esters,[11a,b] *N*-methoxy-*N*-methylamides (Weinreb amides),[11c,d] and imidazolides[11e,f] as acylating agents, yet here the latter reagents furnished the best results. Under optimized conditions an 83:17 mixture of β,δ-diketoester **11** and starting material **13** was isolated, which could only be separated by column chromatography on silica gel with substantial loss of product. Therefore, crude **11** was directly used in the next step, i.e., the lactonization in the presence of DBU. This afforded a mixture of pyrone **14** and ketoester **13** from which the pyrone could easily be separated

(3) (a) Graber, M. A.; Gerwick, W. H. *J. Nat. Prod.* **1998**, *61*, 677−680. (b) Yano, K.; Yokoi, K.; Sato, J.; Oono, J.; Kouda, T.; Ogawa, Y.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 38−43. (c) Takahashi, N.; Suzuki, A.; Tamura, S. *J. Am. Chem. Soc.* **1965**, *87*, 2066−2068.

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(5) Shimamura, H.; Sunazuka, T.; Izuhara, T.; Hirose, T.; Shiomi, K.; Omura, S. *Org. Lett.* **2007**, *9*, 65−67.

(6) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679−680.

(7) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.

(8) (a) Negishi, E.-i.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639−6647. (b) Lipshutz, B. H.; Bulow, G.; Fernandez-Lazaro, F.; Kim, S.-K.; Lowe, R.; Mollard, P.; Stevens, K. L. *J. Am. Chem. Soc.* **1999**, *121*, 11664−11673.

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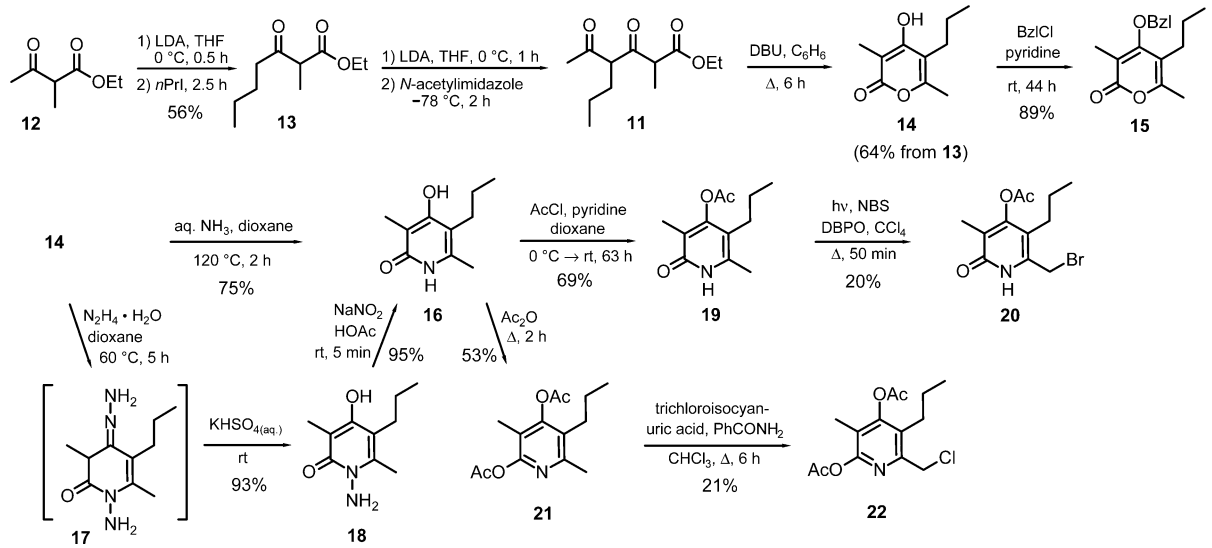
(10) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082−1087.

(11) (a) Spencer, R. W.; Copp, L. J.; Pfister, J. R. *J. Med. Chem.* **1985**, *28*, 1828−1832. (b) Kanazawa, T.; Ohkawa, Y.; Kuda, T.; Minobe, Y.; Tani, T.; Nishizawa, M. *Chem. Pharm. Bull.* **1997**, *45*, 1046−1051. (c) Oster, T. A.; Harris, T. M. *Tetrahedron Lett.* **1983**, *24*, 1851−1854. (d) Wolberg, M.; Ji, A.; Hummel, W.; Müller, M. *Synthesis* **2001**, 937−942. (e) Shone, R. L.; Deason, J. R.; Miyano, M. *J. Org. Chem.* **1986**, *51*, 268−270. (f) Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1996**, *37*, 2997−3000.

SCHEME 2. Synthesis of Different Ring Fragments

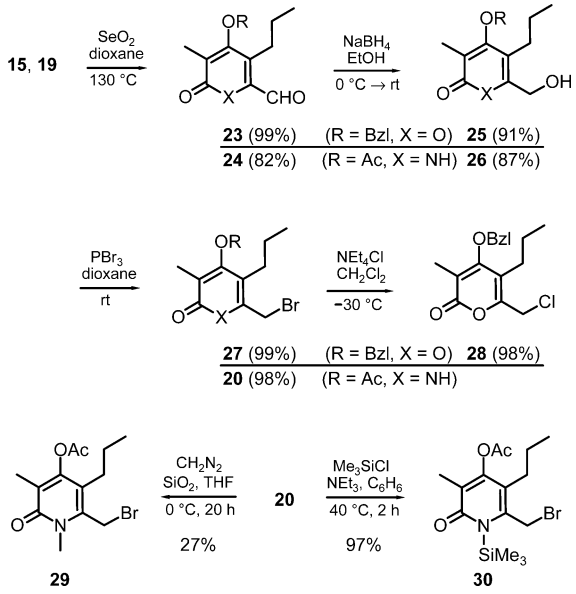


by extraction with saturated $NaHCO_3$ solution.[12] That way pyrone **14** was isolated in a high yield of 64% over the two steps from compound **13**. Next, the 4-hydroxy moiety of **14** was benzoylated to give **15** as a prerequisite for the subsequent functionalization of the methyl substituent at C-6.[13,14] In parallel, pyrone **14** was also transformed into the respective nitrogen analogue **16**.[15] This was achieved by heating **14** with aqueous ammonia in a sealed tube at 120 °C. The same type of reaction smoothly occurred at 60 °C with the more nucleophilic hydrazine to intermediately give hydrazone **17** which was cleaved to *N*-aminopyridone **18** upon acidic workup. Treatment of this compound with nitrous acid under mild conditions then furnished pyridone **16** in 88% overall yield from **14**, thus making this two-step procedure the favorable method. The product was then either mono-acetylated to give the protected pyridone **19** or bis-acetylated to **21**.

The selective functionalization of alkyl substituents at C-6 in α-pyrones similar to compound **15** has been the subject of several studies which revealed that halogenation via radical substitution is possible yet frequently occurs in varying yields.[13,16] Indeed, bromination of compounds **15** and **19** using NBS and dibenzoyl peroxide (DBPO) proceeded rather unselectively thus furnishing only low yields of the desired products, e.g., 20% of compound **20**. Similarly, chlorination of pyridine **21** using trichloroisocyanuric acid[17] afforded 6-chloromethylpyridine **22** in just 21% yield.

Therefore, we turned to a method developed by Hoffmann et al. for the bromination of an ethyl substituent at C-6 of an

SCHEME 3. Improved Functionalization of the 6-Methyl Substituent



α-pyrone comprising oxidation with SeO_2 to form the respective secondary alcohol and subsequent treatment with PBr_3.[13] The oxidation of pyrone **15** and pyridone **19** generated aldehydes **23** and **24**, respectively, which were reduced in an additional reaction step using $NaBH_4$ (Scheme 3). The bromides **20** and **27** were thus obtained in excellent overall yields, and pyrone **27**, after treatment with an excess of NEt_4Cl, furnished the chloride **28**. Finally, the rather acidic secondary amide moiety in **20** was protected by N-silylation with Me_3SiCl to furnish pyridone **30** or by N-methylation with diazomethane in the presence of silica gel which afforded **29** in a low yield due to a large amount of O-methylation. Altogether, the building blocks **20**, **22**, and **27**−**30** with similar skeletons—yet different heterocyclic moieties and leaving groups—were thus efficiently obtained.

Unlike the side chains of the piericidins (**3**) which required a multistep synthesis,[4] the side chain of iromycin A (**1a**) was obtained in just five steps from isobutyraldehyde (Scheme 4). A 1:4 mixture of allyl bromides **31** and **32** was prepared via

(12) The acidity of such 4-hydroxypyran-2-ones is comparable to that of acetic acid: Ferri, D.; Bürgi, T.; Baiker, A. *J. Chem. Soc. Perkin Trans. 2* **2002**, 437−441.

(13) Köster, G.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1987**, 987−990 and references therein.

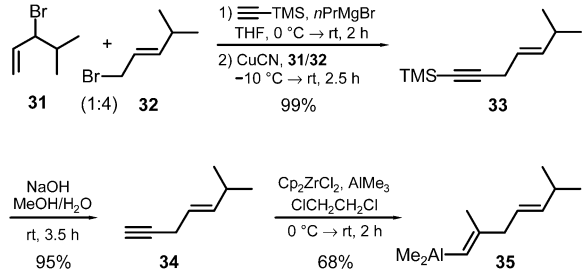
(14) Pyrone **14** could also be acetylated in 69% yield (see Supporting Information), yet this protecting group turned out to be unstable in the subsequent transformations.

(15) (a) Groutas, W. C.; Stanga, M. A.; Brubaker, M. J.; Huang, T. L.; Moi, M. K.; Carroll, R. C. *J. Med. Chem.* **1985**, *28*, 1106−1109. (b) El-Kholy, I. E.; Mishrikey, M. M.; Abdoul-Ela, S. L. *J. Heterocycl. Chem.* **1982**, *19*, 1329−1334.

(16) (a) Bloomer, J. L.; Zaidi, S. M. H.; Strupczewski, J. T.; Brosz, C. S.; Gudzyk, L. A. *J. Org. Chem.* **1974**, *39*, 3615−3616. (b) Bacardit, R.; Moreno-Manas, M.; Pleixats, R. *J. Heterocycl. Chem.* **1982**, *19*, 157−160.

(17) Jeromin, G. E.; Orth, W.; Rapp, B.; Weiss, W. *Chem. Ber.* **1987**, *120*, 649−651.

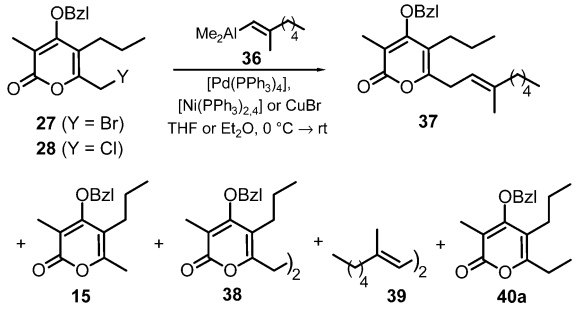
SCHEME 4. Synthesis of the Side Chain Fragment as Alkenylalane



vinylation of the aldehyde with vinylmagnesium bromide[18a] and subsequent treatment of the alcohol with PBr_3.[18b] Interestingly, the copper-catalyzed alkynylation of this mixture furnished a single enyne **33** which was desilylated to afford compound **34**. The carboalumination of this terminal alkyne was performed according to the general procedure of Negishi et al. using zirconocene dichloride as catalyst and 2 equiv of $AlMe_3$.[8a] This excess of $AlMe_3$ caused problems in subsequent cross-coupling reactions when using in-situ prepared alkenylalane. Therefore, the $AlMe_3$ was distilled off and the isolated alkenylalane **35** as solution in hexane could be stored for several weeks at −18 °C.

Attempted Coupling of Ring and Side Chain Fragments under Transition Metal Catalysis. Since alkenylalanes are readily and selectively accessible by hydroalumination[19] and carboalumination[8a,20] of alkynes, their use in carbon−carbon bond forming processes has been studied for a long time. As shown by Negishi et al., 1,3-dienes,[21a,b] 1,4-dienes,[21c,d] and allylarenes[21e] can be formed when treating these alanes with alkenyl halides, allylic electrophiles, and benzyl halides, respectively, in the presence of a palladium catalyst. Nickel catalysts sometimes afford faster conversions,[21f] but stereochemical scrambling was noted as a problem.[21b] Lipshutz et al. demonstrated the higher reactivity of nickel catalysts when performing coupling reactions with various chloromethylarenes, -heteroarenes, and -quinones as electrophiles,[22] and both Pd and Ni have been employed in these transformations toward the synthesis of natural products.[8b,23] Therefore, both transition metals were tried out for the intended coupling of the ring and side chain fragments of iromycin A (**1a**), and preliminary tests were performed using (*E*)-2-methyl-1-heptenyldimethylalane (**36**) as a model substrate (Scheme 5).[24] The 6-bromomethylpyridone **20** turned out to be unstable under these conditions, and

SCHEME 5. Attempted Transition-Metal-Catalyzed Coupling of Ring and Side Chain Fragments



complex mixtures of unidentified products were obtained even when starting from *N*-protected derivatives **29** or **30**. Palladium-catalyzed transformations of pyrone **27** led to smooth debromination to furnish the 6-methylpyrone **15** as the sole product. Using in situ prepared $[Ni(PPh_3)_4]$ as catalyst, **27** underwent a reductive dimerization to furnish compound **38** together with **39**, the product of a homo-coupling of the alkenylalane. The same result was obtained when decreasing the phosphine−nickel ratio to 2:1 or when adding LiCl, even though these changes were reported to favor the formation of cross-coupled as opposed to homo-coupled products.[22] In contrast, minor amounts of the desired product **37** were obtained when switching to chloride **28** as starting material, but still homo-coupling predominated. Finally, pyridine **22** turned out to be rather unreactive in the nickel-catalyzed transformation, and only slow decomposition was observed. These difficulties are presumably caused by the very specific character of these heterocyclic ring fragments in which the C-2−C-6 subunit together with the halomethyl group at C-6 can be seen as a vinylogous α-haloester and, together with the acyloxy group at C-4, resembles a vinylogous acid anhydride. Pyrone **27** might undergo a fast oxidative addition to the metal(0) complexes, but the organometallic species then decomposes either by protiodepalladation, i.e., placement of hydrogen on the pyrone ligand, or under dimerization of the same in the case of nickel.[25]

Besides palladium and nickel complexes, copper(I) salts have rarely been used in cross-coupling reactions of alkenylalanes with allylic electrophiles to form 1,4-dienes,[26a,b] even though alkenylalanes can also undergo oxidative dimerizations with stoichiometric amounts of CuCl to form symmetrical 1,3-dienes and metallic copper.[26c] When treating pyrone **27** with the side chain model, the in situ prepared alane **36**, in the presence of a catalytic amount of CuBr, a smooth conversion occurred; however, a methyl group was transferred to yield solely 6-ethylpyrone **40a** (Scheme 5). Therefore, a quick survey on the transferability of different substituents on alanes was undertaken, for which several alkylvinylalanes were prepared from the respective alkylaluminum chloride and vinylmagnesium

(18) (a) Kaga, H.; Goto, K.; Takahashi, T.; Hino, M.; Tokuhashi, T.; Orito, K. *Tetrahedron* **1996**, *52*, 8451−8470. (b) Jacoby, D.; Célérier, J. P.; Petit, H.; Lhommet, G. *Synthesis* **1990**, 301−304.

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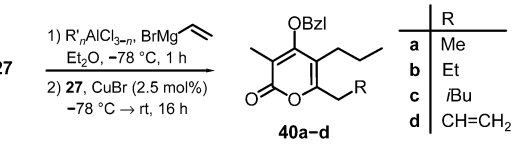
(24) Since alkyl groups are not transferred under these conditions,[21c] crude alkenyldimethylalane stemming from carboalumination of 1-heptyne with an excess of $AlMe_3$ was employed.

(25) For a study on the oxidative addition of benzyl halides to Ni(0) complexes leading to formation of dibenzyl, see: Bartsch, E.; Dinjus, E.; Fischer, R.; Uhlig, E. *Z. Anorg. Allg. Chem.* **1977**, *433*, 5−12. For other examples of protiodepalladations, see: Voigt, K.; von Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521−1534.

(26) (a) Lynd, R. A.; Zweifel, G. *Synthesis* **1974**, 658−659. (b) Flemming, S.; Kabbara, J.; Nickisch, K.; Westermann, J.; Mohr, J. *Synlett* **1995**, 183−185. (c) Zweifel, G.; Miller, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 6678−6679.

TABLE 1. Study on Copper-Catalyzed Cross-Coupling Reactions of 27 with Alanes



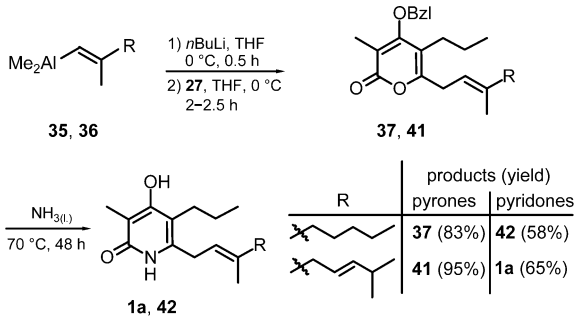
entry	alane, (equiv)[a]	conversion[b] [%]	products	ratio of products[b]
1	$(CH_2{=}CH)AlEt_2$, (4)	94	**40d**, **40b**	51:49
2	$(CH_2{=}CH)Al(iBu)_2$, (4)	53	**40d**, **40c**	63:37
3	$(CH_2{=}CH)_2AlEt$, (2)	34	**40d**, **40b**	100:0
4	$(CH_2{=}CH)_2AlMe$, (2)	100	**40d**, **40a**	100:0

[a] In situ prepared from the respective alkylaluminum chloride and vinylmagnesium bromide. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture.

bromide and then added to a pre-cooled suspension of CuBr and pyrone **27** (Table 1). The results disclosed that the selectivity of vinyl versus alkyl transfer is rather low when using vinyldialkylalanes (entries 1, 2). In contrast, selective vinyl transfer took place starting from divinylalkylalanes, and the respective methylalane was far more reactive than the analogous ethylalane (entries 3, 4). At first glance, these results were contradictory with the outcome of the reaction of alane **36** furnishing product **40a** of a methyl transfer. Yet, when the isolated—thus $AlMe_3$-free—alane **36** was employed, no cross-coupling reaction occurred at all, and the homo-coupled compounds **38** and **39** were the only identified products. The formation of 6-ethylpyrone **40a** in the first experiment must therefore be caused by the remaining $AlMe_3$ in the in situ prepared alane **36**, and both the methyl and the heptenyl groups of the isolated **36** are obviously transferred so slowly that other reaction pathways prevail. The preferred transfer of the alkenyl group from the alanes shown in Table 1 thus seems to be limited to the simple ethenyl group. Altogether, these observations are noteworthy, as transfer of an alkenyl group is generally kinetically favored over an alkyl group exchange in related transformations.[27]

Coupling of the Fragments via Lithium Alkenylalanates and Completion of the Total Synthesis. Before the ascent of transition metal catalysts in carbon−carbon bond forming processes, 1,4-dienes and allylarenes are known to be formed by reaction of the respective halides with lithium alkenyltrialkylalanates. However, yields were moderate, and the reported substrate scope is quite narrow—only covering plain benzyl halides and simple allyl halides that can give just one product.[28] Nevertheless, this method was finally applied in the coupling of ring and side chain fragments of iromycin A, and again, first experiments were performed with the model substrate **36** stemming from carboalumination of 1-heptyne. This alane was treated successively with *n*BuLi to form the lithium alanate and afterward with the respective halide. The reaction with benzyl bromide as model substrate indeed turned out to proceed sluggishly and yielded considerable amounts of 1,2-diphenylethane as byproduct.[28c] Starting from unprotected pyridone **20** and methyl-protected **29** complete decomposition of the ring fragment was observed, and $SiMe_3$-protected **30** was mainly desilylated under these conditions to furnish **20**. Yet, pyrone **27** proved to be a very suitable substrate. After a short screen of solvents including toluene, Et_2O, and THF in combination with reaction temperatures ranging from −30 °C to rt, the desired product **37** was obtained in 83% isolated yield when treating **27** with the alanate prepared from 2 equiv of each, alane **36** and *n*BuLi (Scheme 6). The preparation of **41**, the precursor of iromycin A (**1a**), succeeded in an even higher yield of 95% when the alanate was prepared from 3 equiv of alane **35** and 2 equiv of *n*BuLi. It is obvious that an excess of the latter with respect to the alane must be avoided since lithium organyls rapidly react with pyrone **27** under lithium−bromide exchange. With the coupling of both fragments achieved, the final challenge was to convert the assembled pyrones **37** and **41** into the respective pyridones **1a** and **42**, which was hampered by a pronounced instability of these compounds.[29] Thus, treatment of **41** with hydrazine or aqueous ammonia under conditions which worked well for the analogous transformation of pyrone **14** to pyridone **16** (Scheme 2) led to decomposition or debenzoylation. The balance between a required high reactivity of the nitrogen nucleophile and mild conditions was found in treating the pyrones with liquid ammonia in an autoclave at 70 °C. This, in one step, afforded the desired O—N exchange and the deprotection of the hydroxyl moiety at C-4 of the pyridone ring to furnish the natural product iromycin A (**1a**) and a first non-natural derivative **42**. The properties of synthetic **1a** proved identical in all respects to those of the isolated metabolite.

SCHEME 6. Completion of the Total Synthesis of Iromycin A (1a) and its Analogue 42



Conclusion

In summary, a convergent and efficient total synthesis of iromycin A (**1a**) was developed which furnished this potent NOS inhibitor in a high overall yield of 18% over the nine steps from *β*-ketoester **12**. Crucial for this achievement was a thorough study of the key step of the synthesis: the coupling reaction of 6-bromomethylpyrone **27** with alkenylalanes. Remarkably, this transformation could not be accomplished by any of the sophisticated transition-metal-catalyzed protocols which either led to reductive debromination using Pd catalysts, reductive dimerization of the ring fragment under Ni catalysis, or preferential alkyl transfer in the case of Cu catalysts. Only the rather conventional noncatalyzed procedure involving formation of lithium trialkylalkenyl-alanates resulted in excellent yields

(27) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178−3186. For an example of a copper-catalyzed 1,4-addition to an enone in which a slight variation of the substrate completely inverted this selectivity, see: Lipshutz, B. H.; Dimock, S. H. *J. Org. Chem.* **1991**, *56*, 5761−5763.

(28) (a) Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.* **1976**, *41*, 2214−2215. (b) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215−2217. (c) Baba, S.; Van Horn, D. E.; Negishi, E.-i. *Tetrahedron Lett.* **1976**, *17*, 1927−1930.

(29) All these compounds slowly start to decompose even when stored either neat or in solution at −18 °C.

(up to 95%) of the desired products. On the basis of our experience, it would in certain instances be valuable to examine uncatalyzed couplings of compatible partners early in the screening phase of reaction development in the event a straightforward solution is available. The thus-completed synthesis of **1a** shows the additional advantages of employing cheap and readily available starting materials and reactants and allowing for a flexible modification of both parts of the molecule. With the first non-natural iromycin **42** in hand, work is now in progress to prepare an array of derivatives in order to get more insight into the structure−activity relationship of this family of pyridone metabolites.

Experimental Section

Ethyl 2-Methyl-3-oxo-heptanoate (13). *n*BuLi (95 mL, 0.22 mmol, 2.27 M in hexane) was slowly added at 0 °C to a solution of diisopropylamine (30.5 mL, 22.0 g, 0.218 mol) in THF (380 mL), and the solution was stirred for 30 min. A solution of ethyl 2-methyl-3-oxo-butanoate (**12**, 14.12 g, 97.94 mmol) in THF (5 mL) was added dropwise, and the mixture was stirred for 30 min. Then, *n*-propyl iodide (10.5 mL, 18.3 g, 0.108 mol) in THF (5 mL) was added dropwise at 0 °C, and stirring was continued for 2.5 h. The mixture was treated with concd HCl (12 mL), the phases were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (2 × 20 mL), and the aqueous phases were re-extracted with Et_2O (50 mL). The combined organic phases were dried over $MgSO_4$, then filtered, and concentrated in vacuo. The residue was purified by distillation (90 °C, 8 mbar) to furnish 10.23 g (56%) of *β*-ketoester **13** as a colorless liquid. IR (cm^{-1}, film): 2984, 2961, 2875, 1749, 1716, 1653, 1457, 1377, 1327, 1270, 1239, 1198, 1115, 1069, 1027, 860, 739, 704. ^1H NMR (250 MHz, $CDCl_3$): δ 0.91 (t, ^3J = 6.4 Hz, 3 H), 1.26 (t, ^3J = 7.4 Hz, 3 H), 1.32 (d, ^3J = 6.8 Hz, 3 H), 1.34 (m_c, 2 H), 1.54 (m_c, 2 H), 2.54 (m_c, 2 H), 3.50 (q, ^3J = 6.8 Hz, 1 H), 4.18 (q, ^3J = 7.4 Hz, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 12.5 (+), 13.6 (+), 13.9 (+), 22.0 (−), 25.4 (−), 40.9 (−), 52.6 (+), 61.0 (−), 170.4 (C_{quat}), 205.7 (C_{quat}). MS (EI, 70 eV) *m*/*z* (%): 186 (10) [M^+], 157 (3) [$M^+ - CH_2CH_3$], 141 (8) [$M^+ - OCH_2CH_3$], 102 (28), 85 (100) [$C_5H_9O^+$]. Anal. Calcd (%) for $C_{10}H_{18}O_3$ (186.3): C, 64.49; H 9.74. Found: C, 64.28; H, 9.49.

Ethyl 4-Acetyl-2-methyl-3-oxo-heptanoate (11). *n*BuLi (87 mL, 0.22 mol, 2.5 M in cyclohexane) was slowly added at 0 °C to a solution of diisopropylamine (30.8 mL, 22.2 g, 0.220 mol) in THF (500 mL), and the solution was stirred for 30 min. Ketoester **13** (15.60 g, 83.76 mmol) in THF (10 mL) was added dropwise, and the solution was stirred for 1 h and then cooled to −78 °C. A solution of *N*-acetylimidazole (13.84 g, 0.1257 mol) in THF (150 mL) was added, and stirring was continued for 2 h at −78 °C. The reaction was quenched with saturated NH_4Cl solution and warmed to rt. The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL). The aqueous phases were extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried over $MgSO_4$, then filtered, and concentrated in vacuo to yield 20.84 g of crude diketoester **11** as a brownish oil. Due to partial decomposition on attempted chromatography, the crude product was directly used in the next step. IR (cm^{-1}, film): 3057, 2987, 2963, 2875, 1720, 1700, 1653, 1457, 1379, 1266, 737, 704. ^1H NMR (250 MHz, $CDCl_3$): δ 0.93 (m_c, 3 H), 1.10−1.60 (m, 8 H), 1.68−2.01 (m, 2 H), 2.15 (m_c, 3 H), 3.65 (m_c, 1 H), 3.80−3.96 (m, 1 H), 4.15 (m_c, 2 H). MS (ESI) *m*/*z* (%): 479 (46) [2M + Na]$^+$, 292 (100), 251 (18) [M + Na]$^+$.

4-Hydroxy-3,6-dimethyl-5-propylpyran-2-one (14). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (16.1 mL, 16.4 g, 0.108 mol) was added to a solution of diketoester **11** (20.30 g, 88.92 mmol) in benzene (300 mL), and the mixture was refluxed for 6 h, poured into a saturated $NaHCO_3$ solution (50 mL), and extracted with Et_2O (3 × 200 mL). The combined organic phases were dried over Na_2SO_4, then filtered, and concentrated in vacuo to give 7.552 g of a fraction partially containing ethyl 2-methyl-3-oxo-heptanoate (**13**). The aqueous phase was acidified with concd HCl to pH 2 and extracted with Et_2O (3 × 150 mL). The combined organic phases were dried over Na_2SO_4, then filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (800 g, hexane/EtOAc 2:1 + 5% MeOH) to furnish 9.71 g (64% over 2 steps from **13**) of pyrone **14** (R_f = 0.35) as a colorless solid. Mp: 81 °C. IR (cm^{-1}, KBr): 3205, 2962, 2873, 1669, 1569, 1456, 1223, 1174, 1131, 1056, 945, 761. ^1H NMR (250 MHz, $CDCl_3$): δ 0.92 (t, ^3J = 7.4 Hz, 3 H), 1.49 (m_c, 2 H), 1.99 (s, 3 H), 2.21 (s, 3 H), 2.36 (t, ^3J = 8.0 Hz, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ 8.7 (+), 13.7 (+), 16.9 (+), 22.3 (−), 26.6 (−), 98.4 (C_{quat}), 112.6 (C_{quat}), 155.7 (C_{quat}), 166.4 (C_{quat}), 167.2 (C_{quat}). MS (EI, 70 eV) *m*/*z* (%): 182 (16) [M^+], 154 (16) [$M^+ - C_2H_4$], 127 (9) [$M^+ - C_4H_7$], 125 (18) [$M^+ - C_4H_9$], 86 (20), 84 (35), 57 (53) [$C_3H_5O^+$], 43 (100) [$C_3H_7^+$].

4-Benzoyloxy-3,6-dimethyl-5-propylpyran-2-one (15). A solution of pyrone **14** (5.17 g, 28.4 mmol) and benzoyl chloride (3.63 mL, 4.40 g, 31.3 mmol) in pyridine (50 mL) was stirred for 44 h at rt and then poured into a saturated $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined organic phases were dried over Na_2SO_4, then filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (550 g, hexane/EtOAc 8:1 + 5% MeOH) to yield 7.21 g (89%) of benzoate **15** (R_f = 0.30) as a colorless oil. IR (cm^{-1}, film): 2965, 1743, 1707, 1577, 1387, 1256, 1178, 1114, 1066, 908, 733. ^1H NMR (250 MHz, $CDCl_3$): δ 0.87 (t, ^3J = 7.4 Hz, 3 H), 1.47 (m_c, 2 H), 1.92 (s, 3 H), 2.22 (t, ^3J = 7.4 Hz, 2 H), 2.28 (s, 3 H), 7.54 (m_c, 2 H), 7.70 (m_c, 1 H), 8.15 (m_c, 2 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ 10.3 (+), 13.7 (+), 17.2 (+), 22.7 (−), 27.4 (−), 112.8 (C_{quat}), 113.4 (C_{quat}), 127.7 (C_{quat}), 128.9 (+), 130.2 (+), 134.4 (+), 156.3 (C_{quat}), 159.5 (C_{quat}), 162.6 (C_{quat}), 164.5 (C_{quat}). MS (ESI, MeOH/NH_4OAc): *m*/*z* (%) 573 (46) [2M + H]$^+$, 555 (77) [2M − OH]$^+$, 433 (23), 287 (100) [M + H]$^+$. Anal. Calcd (%) for $C_{17}H_{18}O_4$ (286.3): C, 71.31; H, 6.34. Found: C, 71.12; H, 6.02.

4-Benzoyloxy-6-formyl-3-methyl-5-propylpyran-2-one (23). A mixture of selenium dioxide (6.67 g, 60.1 mmol) and pyrone **15** (9.76 g, 34.1 mmol) in dioxane (200 mL) was heated in a sealed tube to 130 °C. After 5 and 10 h the same amount of selenium dioxide was added (20.0 g, 180 mmol in total), and stirring was continued for another 6 h. The reaction mixture was cooled to rt and filtered over Na_2SO_4/Celite, and the solids were washed with Et_2O (200 mL). The filtrate was concentrated in vacuo to give 10.16 g (99%) of aldehyde **23** as a colorless solid, whose purity was >95%. For analysis a sample was purified by column chromatography on SiO_2 (hexane/EtOAc 4:1, R_f = 0.32). Mp: 97 °C. IR (cm^{-1}, KBr): 3055, 2969, 1748, 1728, 1636, 1266, 1242, 1193, 1177, 1045, 739, 705. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, ^3J = 7.4 Hz, 3 H), 1.54 (sext, ^3J = 7.4 Hz, 2 H), 2.01 (s, 3 H), 2.68 (bs, 2 H), 7.55 (t, ^3J = 7.8 Hz, 2 H), 7.70 (m_c, 1 H), 8.15 (m_c, 2 H), 9.78 (s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ 11.5 (+), 13.7 (+), 23.3 (−), 25.2 (−), 123.4 (−), 124.7 (−), 127.1 (−), 129.1 (+), 130.4 (+), 134.9 (+), 147.2 (−), 157.5 (−), 161.4 (−), 162.4 (−), 183.4 (+). MS (EI, 70 eV) *m*/*z* (%): 300 (6) [M^+], 105 (100), 77 (16). Anal. Calcd (%) for $C_{17}H_{16}O_5$ (300.3): C, 67.99; H, 5.37. Found: C, 67.70; H, 5.24.

4-Benzoyloxy-6-hydroxymethyl-3-methyl-5-propylpyran-2-one (25). $NaBH_4$ (85 mg, 2.2 mmol) was added to a solution of aldehyde **23** (0.562 g, 1.87 mmol) in EtOH (15 mL) at 0 °C, and the mixture was stirred for 4 h at rt. After addition of saturated NH_4Cl solution (10 mL), the mixture was concentrated in vacuo and then extracted with EtOAc (5 × 25 mL). The combined organic phases were dried over Na_2SO_4, then filtered, and concentrated in vacuo. The residue was recrystallized from EtOAc to yield

0.513 g (91%) of alcohol **25** as a colorless solid. Mp: 110 °C. IR (cm^{-1}, KBr): 3423, 2962, 2874, 1746, 1717, 1582, 1243, 1176, 1112, 1046, 1022, 706. ^1H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, $^3J = 7.4$ Hz, 3 H), 1.50 (m_c, 2 H), 1.97 (s, 3 H), 2.30 (m_c, 2 H), 4.52 (s, 2 H), 7.55 (t, $^3J = 7.1$ Hz, 2 H), 7.70 (m_c, 1 H), 8.15 (m_c, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ 10.7 (+), 13.7 (+), 23.4 (−), 26.9 (−), 59.0 (−), 114.3 (−), 115.9 (−), 127.6 (−), 129.0 (+), 130.3 (+), 134.6 (+), 155.8 (−), 159.0 (−), 162.5 (−), 163.8 (−). MS (EI, 70 eV) *m*/*z* (%): 302 (4) [M^+], 105 (100), 77 (16). Anal. Calcd (%) for $C_{17}H_{18}O_5$ (302.3): C, 67.54; H, 6.00. Found: C, 67.61; H, 6.04.

4-Benzoyloxy-6-bromomethyl-3-methyl-5-propylpyran-2-one (27). PBr_3 (0.58 mL, 1.7 g, 6.2 mmol) was added to a solution of alcohol **25** (1.688 g, 5.583 mmol) in dioxane (10 mL) at 40 °C. The mixture was stirred for 30 min at 40 °C and for 15 h at rt, poured into a saturated $NaHCO_3$ solution (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, then filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on SiO_2 (250 g, hexane/EtOAc 5:1) to furnish 2.04 g (>99%) of bromide **27** (R_f = 0.30) as a colorless solid. Mp: 84 °C. IR (cm^{-1}, KBr): 3055, 2964, 2874, 1747, 1718, 1576, 1265, 1178, 1066, 1046, 658. ^1H NMR (250 MHz, $CDCl_3$): δ 0.92 (t, $^3J = 7.4$ Hz, 3 H), 1.60 (m_c, 2 H), 1.97 (s, 3 H), 2.30 (t, $^3J = 7.4$ Hz, 2 H), 4.30 (s, 2 H), 7.58 (t, $^3J = 7.1$ Hz, 2 H), 7.72 (m_c, 1 H), 8.15 (m_c, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ 10.9 (+), 14.06 (+), 22.6 (−), 24.6 (−), 27.6 (−), 115.9 (−), 117.3 (−), 127.4 (−), 129.0 (+), 130.3 (+), 134.6 (+), 152.6 (−), 158.5 (−), 162.4 (−), 163.1 (−). MS (DCI, NH_3) *m*/*z* (%): 748 (38) $[2M + NH_4]^+$, 382 (100) $[M + NH_4]^+$. Anal. Calcd (%) for $C_{17}H_{17}BrO_4$ (365.2): C, 55.91; H, 4.69. Found: C, 56.21; H, 4.40.

(*E*)-1-Trimethylsilyl-6-methylhept-4-en-1-yne (33). *n*-Propylmagnesium bromide (100 mL, 0.10 mol, 1.0 M in Et_2O) was added dropwise at 0 °C to a solution of trimethylsilylacetylene (13.8 mL, 9.59 g, 97.6 mmol) in THF (80 mL), and the mixture was stirred for 2 h at rt. The thus-obtained trimethylsilylethynylmagnesium bromide was transferred by cannula to a precooled (−10 °C) mixture of 3-bromo-4-methylpent-1-ene (**31**), (*E*)-1-bromo-4-methylpent-2-ene (**32**) (10.60 g, 1:4 ratio, 65.01 mmol), and CuCN (0.29 g, 3.2 mmol) in THF (100 mL), and the mixture was stirred for 2.5 h at rt. The reaction mixture was poured into a saturated NH_4Cl solution and extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, then filtered, and concentrated in vacuo (10 mbar). The residue was purified by column chromatography on SiO_2 (150 g, pentane) to yield 11.72 g (99%) of compound **33** (R_f = 0.46) as a colorless liquid. IR (cm^{-1}, film): 3033, 2960, 2177, 1669, 1467, 1420, 1250, 1102, 1050, 1008, 910, 845. ^1H NMR (250 MHz, $CDCl_3$): δ 0.18 (s, 9 H), 0.98 (d, $^3J = 6.6$ Hz, 6 H), 2.28 (m_c, 1 H), 2.94 (d, $^3J = 5.5$ Hz, 2 H), 5.31 (dt, $^3J = 15.5$, $^3J = 5.5$ Hz, 1 H), 5.65 (ddt, $^3J = 15.5$, $^3J = 5.5$ Hz, $^4J = 1.5$ Hz, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ 0.1 (+), 22.3 (+), 23.0 (−), 30.7 (+), 86.0 (C_{quat}), 104.7 (C_{quat}), 120.6 (+), 139.2 (+). MS (EI, 70 eV) *m*/*z* (%): 180 (8) [M^+], 165 (100) [$M^+ - CH_3$], 135 (9) [$M^+ - 3\ CH_3$], 123 (25), 106 (30), 97 (10), 83 (14).

(*E*)-6-Methylhept-4-en-1-yne (34). NaOH (96 mL, 96 mmol, 1.0 M in H_2O) was added at rt to a solution of compound **33** (10.80 g, 58.77 mmol) in MeOH (200 mL), and the mixture was stirred for 3.5 h, poured into a saturated NH_4Cl solution, and extracted with pentane (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, then filtered, and concentrated by careful distillation at atmospheric pressure using a 20 cm Vigreux column. The residue was purified by Kugelrohr distillation (90 °C, 200 mbar) to yield 6.18 g (95%) of enyne **34** as a colorless liquid. IR (cm^{-1}, film): 3309, 2961, 2872, 2252, 1653, 1559, 1466, 1384, 1254, 1056, 847, 735. ^1H NMR (250 MHz, $CDCl_3$): δ 0.99 (d, $^3J = 6.6$ Hz, 6 H), 2.05 (m_c, 1 H), 2.30 (m_c, 1 H), 2.88 (m_c, 2 H), 5.31 (dt, $^3J = 15.5$, $^3J = 5.5$ Hz, 1 H), 5.65 (ddt, $^3J = 15.5$, $^3J = 5.5$ Hz, $^4J = 1.5$ Hz, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ 21.5 (−), 22.2 (+), 30.7 (+), 69.7 (+), 82.1 (C_{quat}), 120.4 (+), 139.4 (+).

(*E*,*E*)-2,6-Dimethylhepta-1,4-dienyldimethylalane (35). Cp_2ZrCl_2 (0.400 g, 1.37 mmol) was treated at 0 °C with $AlMe_3$ (6.92 mL, 14 mmol, 2.0 M in hexane, **caution**: **pyrophoric!**), and the solvent was removed in vacuo. 1,2-Dichloroethane (5 mL) was added, and the solution was stirred for 30 min at 0 °C. A solution of enyne **34** (0.75 g, 6.9 mmol) in 1,2-dichloroethane (10 mL) was added dropwise, and the mixture was stirred for 2 h at rt. At this point, GC analysis of a hydrolyzed aliquot showed complete consumption of the enyne. The solvent and the excess of $AlMe_3$ were removed in vacuo, and hexane (1 mL) was added at 0 °C to precipitate the zirconium salts. The mixture was filtered through a frit, and the solids were washed with hexane (1 mL). The filtrate was concentrated in vacuo to furnish 0.85 g (68%) of alane **35** as a yellow oil whose purity was >95% as determined by GC analysis of a hydrolyzed aliquot. ^1H NMR (250 MHz, $CDCl_3$): δ −0.78 (s, 6 H), 0.98 (d, $^3J = 6.6$ Hz, 6 H), 2.01 (s, 3 H), 2.30 (m_c, 1 H), 2.92 (d, $^3J = 5.0$ Hz, 2 H), 5.26−5.54 (m, 3 H).

4-Benzoyloxy-6-[(*E*,*E*)-3,7-dimethylocta-2,5-dienyl]-3-methyl-5-propylpyran-2-one (41). *n*BuLi (0.39 mL, 0.83 mmol, 2.13 M in hexane) was added to a solution of alane **35** (1.23 mL, 1.2 mmol, 1.0 M in hexane) in THF (1.0 mL) at 0 °C, and the mixture was stirred for 30 min. A solution of bromide **27** (150.0 mg, 0.411 mmol) in THF (2.0 mL) was slowly added at 0 °C, and stirring was continued for 2 h. The reaction mixture was poured into a saturated NH_4Cl solution (3 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, then filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on SiO_2 (10 g, hexane/EtOAc 6:1) to yield 0.16 g (95%) of pyrone **41** (R_f = 0.45) as a colorless oil. IR (cm^{-1}, film): 2963, 1747, 1714, 1576, 1457, 1374, 1243, 1108, 1063, 910, 733. ^1H NMR (250 MHz, $CDCl_3$): δ 0.85 (t, $^3J = 7.4$ Hz, 3 H), 0.95 (d, $^3J = 7.1$ Hz, 6 H), 1.46 (m_c, 2 H), 1.66 (s, 3 H), 1.93 (s, 3 H), 2.23 (m_c, 3 H), 2.65 (d, $^3J = 5.3$ Hz, 2 H), 3.27 (d, $^3J = 7.0$ Hz, 2 H), 5.20−5.50 (m, 3 H), 7.56 (t, $^3J = 7.1$ Hz, 2 H), 7.70 (m_c, 1 H), 8.15 (m_c, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ 10.5 (+), 13.9 (+), 16.3 (+), 22.6 (+, 2 C), 23.2 (−), 27.4 (−), 30.3 (−), 31.0 (+), 42.7 (−), 112.6 (−), 113.6 (−), 118.1 (+), 124.2 (+), 127.8 (−), 128.9 (+), 130.3 (+), 134.4 (+), 137.9 (−), 139.8 (+), 158.7 (−), 159.5 (−), 162.6 (−), 164.6 (−). MS (ESI) *m*/*z* (%): 839 (100) $[2M + Na]^+$, 431 (21) $[M + Na]^+$, 409 (1) $[M + H^+]$.

4-Hydroxy-6-[(*E*,*E*)-3,7-dimethylocta-2,5-dienyl]-3-methyl-5-propyl-1*H*-pyridin-2-one (1a). In an autoclave a mixture of pyrone **41** (60.0 mg, 0.147 mmol) and liquid NH_3 (15 mL) was stirred for 48 h at 70 °C. After the mixture cooled to rt, the NH_3 was carefully evaporated, and the residue was diluted with $KHSO_4$ solution (1.0 M, 3 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, then filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on SiO_2 (8 g, hexane/EtOAc 2:1 + 1% HOAc) to yield 28.8 mg (65%) of pyridone **1a** (R_f = 0.38). All analytical data were consistent with the data of iromycin A (**1a**) isolated from *Streptomyces* sp.[1]

Acknowledgment. This work was financially supported by the Deutsche Forschungsgemeinschaft (SFB 416, Project B14). P.v.Z. is grateful to Prof. Armin de Meijere for his continuing support.

Supporting Information Available: Description of the attempted synthesis of iromycin A along path A; general experimental methods; experimental procedures and characterization data of compounds **8**, **16**, **18**−**22**, **24**, **26**, **28**−**30**, **36**, **37**, **42**, **44**−**47**, **49**, and **50**; ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070327J