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Syntheses of the Hexahydroindene Cores of Indanomycin and Stawamycin by Combinations of Iridium-Catalyzed Asymmetric Allylic Alkylations and Intramolecular Diels–Alder Reactions

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Abstract: Short and concise syntheses of the hexahydroindene cores of the antibiotics indanomycin (X-14547 A) and stawamycin are presented. Key methods used are an asymmetric iridium-catalyzed allylic alkylation, a modified Julia olefination, a Suzuki–Miyaura coupling, and an intramolecular Diels–Alder reaction.

Keywords: alkylation · Diels–Alder reaction · hexahydroindenes · iridium · Julia olefination · Suzuki–Miyaura coupling

Introduction

The enantioselective Ir-catalyzed allylic substitution is a powerful tool in organic synthesis.[1] We are interested in widening the scope of this method by exploration of new allylic substrates and nucleophiles as well as application of the substitution products in natural products synthesis. Herein, we present a combination of the Ir-catalyzed allylic alkylation with the Julia–Kocienski olefination;[2] this method was applied in very short and efficient syntheses of the hexahydroindene cores of the antibiotics indanomycin and stawamycin (Figure 1).

Indanomycin was isolated from the fermentation broth of *Streptomyces antibioticus* and exhibits antibiotic activity against Gram-positive bacteria.[3] Its relative and absolute configuration was determined by X-ray crystal-structure analysis.[3c] stawamycin was also isolated from a *Streptomyces* strain and has shown moderate inhibitory activity against Epstein–Barr virus BZLF1 transcription factor.[4] stawamycin was obtained as an amorphous solid; its structure was determined by NMR spectroscopy, however, the relative configurations of the hydroxylated centers remain unknown.

Up to now, four total syntheses of indanomycin have been reported by the groups of Nicolaou,[5] Ley,[6] Roush,[7] and Burke.[8] The synthesis of a building block representing the hexahydroindene core of stawamycin was described by Dias et al.[9] The key step of all syntheses is an intramolecular Diels–Alder reaction, which has been considered to be a step in the biosynthesis of indanomycin.[10] The previous syntheses were carried out at a time when the methodology of acyclic stereocontrol was not yet far developed. Accordingly, many steps were required for the syntheses of the cyclization precursors. Herein, we now describe a fully stereocontrolled approach based on asymmetric catalysis, which allows the cyclization precursors of both targets to be available in only four steps.

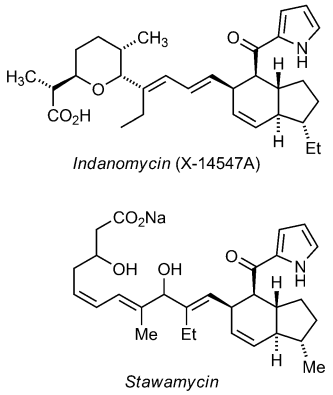

Figure 1. Antibiotics containing a hexahydroindene moiety.

The concept of our synthesis of the *trans*-fused hexahydroindene ring system is outlined in Scheme 1. The key step is an intramolecular Diels–Alder reaction, yielding the hexahydroindene-core structure of stawa- and indanomycin with the desired relative configuration.[11] The chiral linchpin unit of the precursor was envisaged to be obtained by an enantioselective Ir-catalyzed allylic alkylation with a heteroaromatic sulfone as nucleophile. This would allow the conjugated diene to be constructed with high *E* selectivity by Julia-type olefination. The enoate moiety was planned to be introduced by selective hydroboration of the vinyl group, followed by Suzuki–Miyaura coupling with a 3-haloacrylate.

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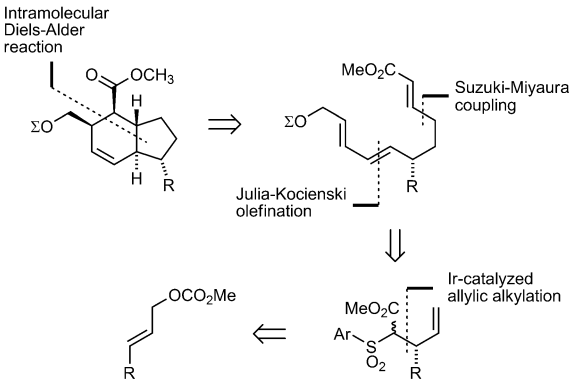


Scheme 1. Retrosynthetic concept (Σ = protecting group).

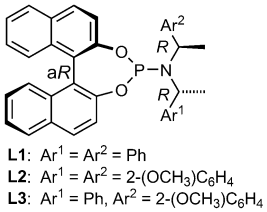


Figure 2. Phosphoramidites used for Ir-catalyzed allylic substitutions.

Results and Discussion

The pronucleophile **Nu1** was introduced by Trost et al. and used in a Pd-catalyzed allylic alkylation with 1,3-dimethylallyl ethyl carbonate in conjunction with a total synthesis of amphidinolide A.[12] We have now tested its applicability in the asymmetric Ir-catalyzed allylic substitution (Scheme 2). Methyl carbonates **1a–c** were used as substrates. The phosphoramidites[13] **L1–L3** with *R*,*R*,a*R* configuration were employed as chiral ligands (Figure 2); it was anticipated[1] that these would induce the desired configuration of the substitution products. "Salt-free" reaction conditions, that is, the use of the conjugate acid of the nucleophile in combination with only a catalytic amount of base, were employed throughout.[14] When initial tests with **Nu1** gave encouraging results, the sulfone **Nu2** was included into the test set (Table 1). However, this was found to be less reactive and gave lower yields than **Nu1**. Reactions with **Nu2** only gave complete conversion in conjunction with the particularly active ligand **L2**.

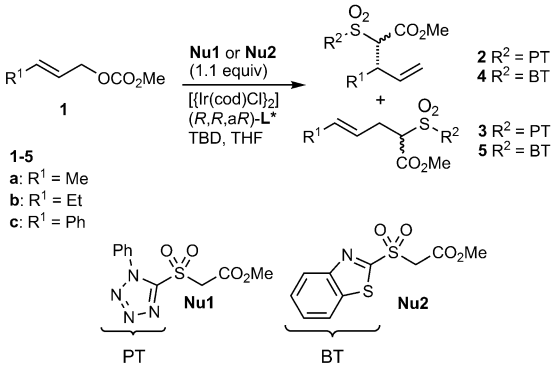
The methoxycarbonyl group, which was required as auxiliary group to reach sufficient acidity in the allylic substitution, was removed after the alkylation by Krapcho demethoxycarbonylation (Scheme 3) by using conditions (NaCl, H_2O, DMSO, 150 °C)[15] that have been previously applied for related substrates by the Trost group.[12] Several unidentified side products were observed, which could be suppressed in the case of the tetrazolylsulfones **2** by omitting NaCl from the reaction mixtures, while this additive was required for the reactions of the benzothiazolylsulfones, because otherwise no reaction occurred. Finally, the sulfones **6** and **7** were obtained in yields of 63–82 %.

The Julia–Kocienski olefinations of the O-protected aldehydes **8a** and **8b**[16] with the sulfones **6** and **7** were carried out with 1,2-dimethoxyethane (DME) as solvent and KHMDS or LiHMDS (HMDS = hexamethyl disilazide) as base at −78 °C. In each case the *E* isomer was obtained with

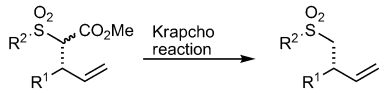
Table 1. Results of the allylic alkylations according to Scheme 2.

Entry	Carbonate	Pronucleophile	Products	L*	Catalyst [mol %][a]	*t* [h]	*T* [°C]	Yield [%][b]	Regioselectivity[c]	*ee* [%][d]
1	**1a**	**Nu1**	**2a+3a**	**L1**	2	72	50	86[e]	91:9	95
2	**1a**	**Nu1**	**2a+3a**	**L2**	1	3.5	50	90	91:9	95.5
3	**1a**	**Nu1**	**2a+3a**	**L3**	2	3.5	RT	92	93:7	93
4	**1b**	**Nu1**	**2b+3b**	**L2**	2	2.5	40	93	87:13	92
5	**1b**	**Nu1**	**2b+3b**	**L3**	4	3	50	91	90:10	91
6	**1c**	**Nu1**	**2c+3c**	**L2**	4	5	RT	89	93:7	97.5
7	**1a**	**Nu2**	**4a+5a**	**L2**	4	2.5	RT	93	95:5	96
8	**1b**	**Nu2**	**4b+5b**	**L2**	4	3	50	77	86:14	97

[a] The catalyst was prepared from [{Ir(cod)Cl}$_2$] (2 mol %), **L*** (4 mol %), and TBD (8 mol %). [b] Combined yield of regioisomers. [c] Ratio of regioisomers (**2**/**3** or **4**/**5**), determined by ^{1}H NMR spectroscopy of the crude product. [d] Determined by HPLC after demethoxycarbonylation.



Scheme 2. Ir-catalyzed allylic alkylation (TBD = 1,5,7-triazabicyclo-[4.4.0]dec-5-ene).



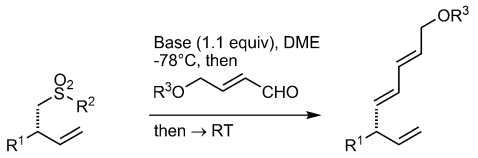
2a: R^1 = Me, R^2 = PT
2b: R^1 = Et, R^2 = PT
2c: R^1 = Ph, R^2 = PT
4a: R^1 = Me, R^2 = BT
4b: R^1 = Et, R^2 = BT

6a: R^1 = Me, R^2 = PT, 82%
6b: R^1 = Et, R^2 = PT, 82%
6c: R^1 = Ph, R^2 = PT, 63%
7a: R^1 = Me, R^2 = BT, 72%
7b: R^1 = Et, R^2 = BT, 76%

Scheme 3. Demethoxycarbonylation using the Krapcho reaction.

a purity of ≈90% (Table 2). The minor component could not be separated. Its tentative structural assignment as *Z* isomer is supported by, in every case, a clearly discernable

Table 2. Julia–Kocienski olefination (PMB = *p*-methoxybenzyl).



6a: R^1 = Me, R^2 = PT
6b: R^1 = Et, R^2 = PT
7a: R^1 = Me, R^2 = BT
7b: R^1 = Et, R^2 = BT

8a: R^3 = $SiPh_2tBu$
8b: R^3 = PMB

9a: R^1 = Me, R^3 = $SiPh_2tBu$
9b: R^1 = Et, R^3 = $SiPh_2tBu$
10a: R^1 = Me, R^3 = PMB
10b: R^1 = Et, R^3 = PMB

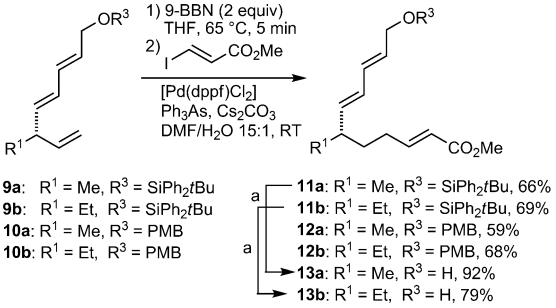
Entry	Aldehyde ([equiv])	Sulfone	Base	Product	*E*/*Z*[a]	Yield [%]
1	**8a** (1.0)	**6a**	KHMDS	**9a**	90:10	54 (75)[b]
2[c]	**8a** (1.0)	**6a**	KHMDS	**9a**	81:19	55 (73)[b]
3	**8a** (1.1)	**6a**	LiHMDS	**9a**	88:12	82
4	**8a** (1.1)	**7a**	KHMDS	**9a**	n.d.	80
5	**8a** (1.0)	**6b**	KHMDS	**9b**	84:16	54 (92)[b]
6	**8a** (1.0)	**6b**	LiHMDS	**9b**	93:7	97
7[c]	**8b** (1.1)	**6a**	KHMDS	**10a**	69:31	58 (73)[b]
8	**8b** (1.0)	**6a**	KHMDS	**10a**	88:12	47
9	**8b** (1.0)	**6a**	LiHMDS	**10a**	84:16	71
10	**8b** (1.5)	**6a**	LiHMDS	**10a**	88:12	88
11	**8b** (1.1)	**7a**	KHMDS	**10a**	n.d.	80
12	**8b** (1.0)	**6b**	LiHMDS	**10b**	85:15	93
13	**8b** (1.0)	**7b**	LiHMDS	**10b**	89:11	83

[a] Determined by ^{1}H NMR spectroscopy. [b] Incomplete conversion, corrected yield in brackets. [c] The reaction was carried out with THF as solvent. n.d. = not determined.

^{13}C NMR resonance of R^1–*C*H upfield by $\delta \approx 5$ ppm from the corresponding signal of the *E* isomer (**9** or **10**). Since the heteroarylsulfones were the more valuable components, an excess of sulfone was avoided. With LiHMDS superior results with respect to conversion and yield were obtained. By using KHMDS as base, the reaction with **8a** proceeded with high *E* selectivity, however, conversion was modest (entries 1, 2, 5, 7, and 8). In the reactions with aldehyde **8b**, the *E*/*Z* ratios were slightly lower than those obtained with the more bulky **8a**.

According to our synthetic route, hydroboration selectively at the vinyl group of the trienes **9** and **10**, as described in Table 2, was required. This was accomplished with 9-borabicyclo[3.3.1]nonan (9-BBN) after some experimentation. As was previously observed with other trienes,[17] the best results were obtained with a reaction time of 5 min (Scheme 4). For the Suzuki–Miyaura coupling,[18] methyl (2*E*)-3-iodoacrylate[19] served as coupling partner in conjunction with [Pd(dppf)Cl_2]/Ph_3As as catalyst and Cs_2CO_3 as base (Scheme 4).[20] The trienes **11** and **12** were obtained in reasonable yields; they proved to be sensitive to air and were stored under argon at −20 °C. The free alcohols **13a** and **b** were prepared from the *t*BuPh_2Si-protected substrates **11** by treatment with *n*Bu_4NF.

The intramolecular Diels–Alder (IMDA) reaction was first carried out under thermal conditions, as previously



9a: R^1 = Me, R^3 = $SiPh_2tBu$
9b: R^1 = Et, R^3 = $SiPh_2tBu$
10a: R^1 = Me, R^3 = PMB
10b: R^1 = Et, R^3 = PMB

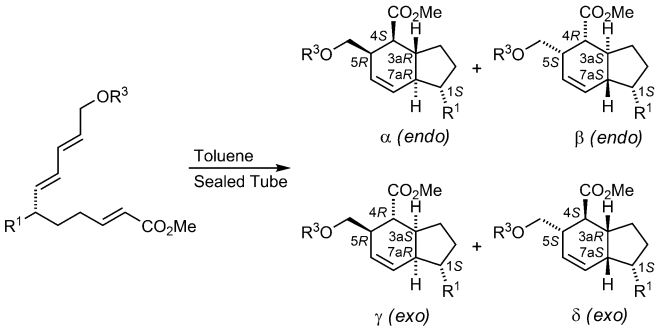
a
a

11a: R^1 = Me, R^3 = $SiPh_2tBu$, 66%
11b: R^1 = Et, R^3 = $SiPh_2tBu$, 69%
12a: R^1 = Me, R^3 = PMB, 59%
12b: R^1 = Et, R^3 = PMB, 68%
13a: R^1 = Me, R^3 = H, 92%
13b: R^1 = Et, R^3 = H, 79%

Scheme 4. Hydroboration/Suzuki–Miyaura coupling (a: *n*Bu_4NF, THF, RT).

used by Nicolaou et al. (toluene, sealed tube, temp. > 100 °C; Table 3).[5] Isomerically pure products could not be isolated, however, column chromatography yielded two fractions in all cases. The major fraction contained a mixture of the two *endo* products (α + β), the individual ratio of which (compare Table 3) could be determined by NMR spectroscopy.[21] The minor fraction contained a mixture of the two *exo* products (γ + δ); their individual configurations were not assigned. The *endo* and *exo* configuration was determined by treatment of products **14** with tetrabutylammonium fluoride (TBAF) to effect desilylation (Scheme 5), which gave lactones **17** from the *endo* products and hydroxy esters **18**

Table 3. Thermal Diels–Alder reaction.

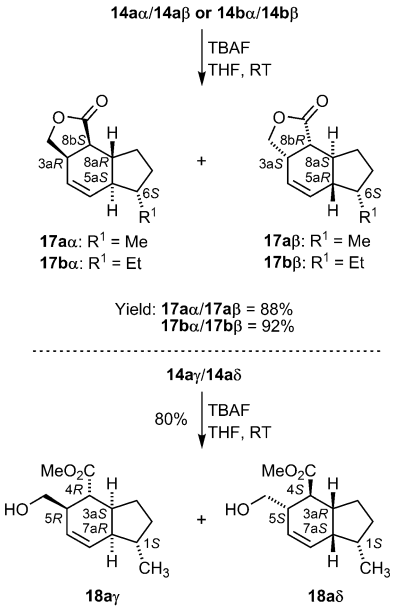


11a: R^1 = Me, R^3 = $SiPh_2tBu$
11b: R^1 = Et, R^3 = $SiPh_2tBu$
12a: R^1 = Me, R^3 = PMB
12b: R^1 = Et, R^3 = PMB
13b: R^1 = Et, R^3 = H

14a: R^1 = Me, R^3 = $SiPh_2tBu$
14b: R^1 = Et, R^3 = $SiPh_2tBu$
15a: R^1 = Me, R^3 = PMB
15b: R^1 = Et, R^3 = PMB
16b: R^1 = Et, R^3 = H
17b: see Table 4

Entry	Starting material	*T* [°C]	*t* [h]	*endo*/*exo*[a]	α/β[b]	Yield [%][c]
1	**11a**	125	63	5.1:1	2.4:1	60
2	**11b**	130	48	3:1	4:1	85
3	**11b**	100	96	5:1	4:1	50 (86)[d]
4	**11b**	160	25	6:1	1:1	50
5	**12a**	130	60	3.6:1	3.2:1	90
6	**12b**	130	52	4.2:1	8:1	88
7	**13b**	130	63	3.4:1	7:1[e]	74

[a] Based on isolated yields. [b] Determined by ^{1}H NMR (**14a** and **15a**) or ^{13}C NMR spectroscopy (**14b**, **15b**, and **17b**). The major isomer possesses the 1*S*,3a*R*,4*S*,5*R*,7a*R* configuration (α). [c] Combined isolated yields. [d] Corrected yield. [e] Spontaneous lactonization to **17b** occurred.



Scheme 5. Desilylation of **14a** and **14b**; upper part: *endo* isomers, lower part: *exo* isomers.

from the *exo* products in high yields. The configurations of the PMB derivatives **15** were determined by analogy of the NMR spectra of **14** and **15**.

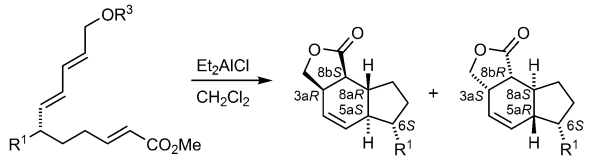
The following aspects of the results described in Table 3 are worth noting. a) The *endo*/*exo* ratio was within the range previously reported for IMDA reactions yielding hexahydroindenes.[5–9,11] b) The *endo*/*exo* selectivity was found to be almost independent of the reaction temperature (entries 3 and 4). c) The IMDA reactions of the fully protected triene **12b** and the triene **13b**, containing a OH group, proceeded with the same facial selectivity (α/β); in the last case spontaneous cyclization of the primarily formed *endo*-**16b** (not observed) to the lactone **17b** (isolated) occurred.[22]

Lewis acid catalyzed Diels–Alder reactions, anticipated to display improved stereoselectivities, were investigated next (Table 4). The *t*BuPh$_2$Si-protected substrates **11** gave rise to decomposition. The PMB-protected trienes **12** and the alcohols **13** tolerated Et$_2$AlCl as Lewis acid and gave diastereomeric lactones **17** as products in modest yields.[21]

As obvious from Table 4, diastereoselectivities were excellent for the ethyl but unsatisfactory for the methyl derivatives. To improve facial selection at the enoate moiety, a chiral auxiliary was introduced. (*R*)-Pantolactone was selected, which was known to give rise to high degrees of diastereoselectivity in intermolecular Diels–Alder reactions, favoring α_{Re}-face attack at the enoate moiety, as required here.[23] The requisite enoate **19** (Scheme 6) was readily prepared.[23b] Suzuki–Miyaura coupling with the PMB-protected substrates **10** gave the trienoates **20** (Scheme 6).

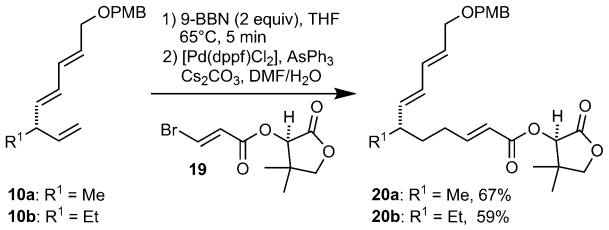
The Et$_2$AlCl-catalyzed IMDA reaction yielded the lactones **17** as the only isolable products (Scheme 7). Judged by the intermolecular reaction of **19** and cyclopentadiene,[23]

Table 4. Et$_2$AlCl-catalyzed IMDA reaction.

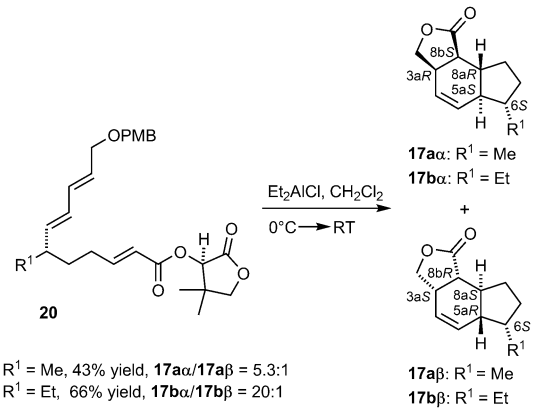


Entry	Starting material	Et$_2$AlCl [equiv]	*T* [°C]	*t* [h]	α/β[a]	Yield [%]
1	**12a**	2	−30→RT	60	2.5:1	41
2	**12b**	5	0→RT	53	9:1	35
3	**13a**	2	−30→RT	60	2.7:1	58
4	**13b**	3	0→RT	21	9:1	41

[a] Determined by ^{1}H NMR (**17a**) or ^{13}C NMR spectroscopy (**17b**).



Scheme 6. Suzuki–Miyaura coupling with 3-*O*-(bromoacryloyl)-(*R*)-pantolactone.



Scheme 7. IMDA reaction with esters of (*R*)-pantolactone.

the cyclization in Scheme 7 represents the matched case. Compared to all other cyclizations leading to lactone **17aα**, the facial selectivity was significantly improved.

In the text above, routes using various protecting and auxiliary groups are described. The following routes most efficiently access the target lactones **17**. The preferred route to **17aα** involves allylic alkylation of **1a** with **Nu1** (Table 1, entry 3), demethoxycarbonylation to give **6a**, Julia-Kocienski olefination of **6a** with **8b** to give **10a** (Table 2, entry 10), Suzuki–Miyaura coupling with **19** to give **20a**, and Et$_2$AlCl-catalyzed IMDA reaction yielding **17a** with a 5:1 diastereo-

selectivity and an overall yield of 19%. The lactone **17bα** is best obtained by allylic alkylation of **1b** with **Nu1** (Table 1, entry 4), demethoxycarbonylation, olefination with **8b** (Table 2, entry 12), Suzuki–Miyaura coupling with **19**, and Et_2AlCl-catalyzed IMDA reaction. This route provides **17b** in 28% overall yield and a diastereofacial selectivity of 20:1. To test the reproducibility, *ent*-**17aα** was also prepared, employing ligand (*S*,*S*,a*S*)-**L2** in the allylic alkylation step.

Conclusion

We have developed a five-step sequence to access the hexahydroindene core present in the antibiotics stawamycin and indanomycin. Highly enantioselective iridium-catalyzed asymmetric allylic alkylations with an α-sulfonylacetic ester as nucleophile served as source of chirality. Subsequent Krapcho reaction and *E*-selective Julia–Kocienski olefination gave a triene that was suitable for one-pot hydroboration with 9-BBN, which proceeded selectively at the vinyl group, and Suzuki–Miyaura coupling generated the diene/enoate precursor of the subsequent intramolecular Diels–Alder reaction. The reaction was controlled by (*R*)-pantolactone as chiral auxiliary and proceeded upon Lewis acid catalysis with good to excellent diastereoselectivity and simultaneous in situ removal of the protecting group and the chiral auxiliary.

Experimental Section

General procedure 1—iridium-catalyzed allylic alkylation: Under an atmosphere of argon, a solution of [{Ir(cod)Cl}$_2$] (2 mol%), **L*** (4 mol%), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 8 mol%) in dry THF was stirred at RT for 5 min (**L2**), 30 min (**L3**), or 90 min (**L1**). Then, carbonate **1** (1 equiv) and pronucleophile **Nu1** or **Nu2** (1.1 equiv) were added, and the solution was stirred at the temperature stated in Table 1 until TLC monitoring showed complete conversion. The solvent was removed in vacuo, and the ratio of regioisomers **2**/**3** or **4**/**5** was determined by ^{1}H NMR spectroscopy of the crude product. Purification by flash chromatography yielded the branched alkylation products **2** or **4** as a mixture of diastereoisomers (1:1) accompanied by the linear alkylation products **3** or **5**, which could not be separated by chromatography. The mixtures of isomers were carried on to the next step.

General procedure 2—Krapcho demethoxycarbonylation: Water (9% *v*/*v*) or NaCl (1.5 equiv) was added to a solution of **2** or **4** (1 equiv) in DMSO, and the resulting mixture was heated at 150°C until TLC monitoring indicated complete conversion. After cooling to RT, water was added, and the solution was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography yielded **6** or **7**. The enantiomeric excesses of **6** or **7** were determined by chiral HPLC. In all cases, the branched sulfones were accompanied by the corresponding linear sulfones, which could not be separated by chromatography. The mixtures of isomers were carried on to the next step.

General procedure 3—Julia–Kocienski olefination (Barbier conditions): LiHMDS (1.1 equiv, 1 M in toluene) was added dropwise to a solution of **6** or **7** (1 equiv) and **8** (1–1.5 equiv) in dry DME at −78°C. The solution was allowed to warm to RT overnight. Water was added, and the solution was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography yielded **9** or **10**. The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy. In all cases, the branched dienes **9** or **10** were accompanied by the corresponding linear dienes, which could not be separated by chromatography. The mixtures of isomers were carried on to the next step.

General procedure 4—Suzuki–Miyaura reaction: Under an atmosphere of argon, a solution of diene **9** or **10** (1.0 equiv) and 9-BBN (2 equiv) in dry THF (2 mL mmol^{-1}) was heated at 65°C for 5 min (solution A). In a separate flask, a suspension of [Pd(dppf)Cl$_2$] (5 mol%), Ph_3As (10 mol%), Cs_2CO_3 (1.8 equiv), and the alkenyl halide (1.1 equiv) in DMF/H_2O (15:1, 2.5 mL mmol^{-1}, degassed with helium) was vigorously stirred for 15 min under an atmosphere of argon. At RT, solution A was added, and the resulting mixture was stirred for 16 h. Then, water was added, and the solution was extracted with diethyl ether, dried over $MgSO_4$, and concentrated in vacuo. The residue was subjected to flash chromatography to yield **11**, **12** or **19**. In all cases, the coupling product contained *Z* isomers (resulting from the olefination), and impurities derived from the linear isomers were separated off.

General procedure 5—thermal intramolecular Diels–Alder reaction: Under an atmosphere of argon, a solution of **11** or **12** in dry toluene (degassed with argon) was heated at the temperature stated in Table 4 in a sealed tube until TLC monitoring indicated complete conversion. The solution was concentrated in vacuo, and the residue was subjected to flash chromatography to yield two fractions of cycloaddition products **14** or **15**. The *endo*/*exo* ratio was determined from the isolated yields; the ratio α/β was determined by NMR spectroscopy.

General procedure 6—Lewis acid catalyzed intramolecular Diels–Alder reaction: Et_2AlCl (1.8 M in toluene, 2–5 equiv) was added dropwise to a solution of **12**, **13** or **19** (1 equiv) in dry CH_2Cl_2 at the stated temperature. The solution was allowed to warm to RT and stirred until TLC monitoring indicated complete conversion. Water was added, and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography yielded lactones **17** as a mixture of diastereoisomers. The ratio α/β was determined by NMR spectroscopy.

For experimental details and analytical data, see the Supporting Information.

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