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Stereoselective Synthesis of Ezetimibe via Cross-Metathesis of Homoallylalcohols and α-Methylidene-β-Lactams

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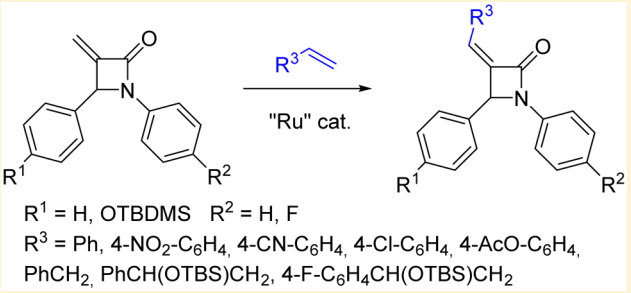
Supporting Information

ABSTRACT: Ru-catalyzed cross-metathesis (CM) reaction between β-arylated α-methylidene-β-lactams and terminal olefins was developed. The CM reaction is effectively catalyzed with Hoveyda−Grubbs second-generation catalyst affording corresponding α-alkylidene-β-aryl-β-lactams in good isolated yields (41−83%) with exclusive *Z*-selectivity. The developed protocol was successfully applied for stereoselective preparation of Ezetimibe, the commercial cholesterol absorption inhibitor.



INTRODUCTION

β-Lactam scaffold is the common structural feature of a number of compounds with broad pharmacological profile.[1] In addition to their importance as bioactive compounds, β-lactams also serve as valuable building blocks in organic synthesis for the preparation of nonproteinogenic β-amino acids, alkaloids, macrolides, toxoids, etc.[2] Ezetimibe, (3*R*,4*S*)-4-(4-hydroxyphenyl)-1-(4-fluorophenyl)-3-[(*S*)-3-hydroxy-3-(4-fluorophenyl)-propyl]azetidine-2-on], is one example from the family of the β-lactam derived pharmaceuticals and is marketed as blockbuster drugs Zetia or Ezetrol.[3] It is a strong cholesterol absorption inhibitor reducing LDL concentration. Despite the fact that a number of synthetic approaches have been developed for its preparation,[4] there are still other pathways that have not been explored yet. In this respect we envisioned that a stereoselective synthesis of Ezetimibe could be based on cross-metathesis (CM) reaction as depicted in retrosynthesis in Scheme 1. The crucial step of the construction of the Ezetimibe framework was assumed to be based on CM of a α-methylene-β-lactam building block (**1b**) with enantiomerically enriched homoallylic alcohols (**2o**). The former could be prepared by Kinugasa reaction[5] or by asymmetric allylic amination of Baylis−Hillman derivatives followed by lactamization.[4b] The latter could come from enantioselective allylation of 4-fluorobenzaldehyde.[6]

The pioneering work showing that α-methylidene-β-lactams could be used for synthesis of α-alkylidene-β-lactams by using CM[7] was reported by Howell and co-workers in 2009.[8] However, only one example of CM of β-substituted α-methylidene-β-lactam was presented. Since then only one more example of CM of α-methylidene-β-lactams has been reported describing the reaction of β-phenyl-α-methylidene-β-lactam with 1-hexene giving β-phenyl-α-hexylidene-β-lactam as a mixture of *E*/*Z* isomers.[4b] To date, no systematic study regarding reactivity of arylated α-methylidene-β-lactams in CM has been undertaken, despite the fact that such a reaction could provide access to synthetically interesting intermediates. In view of the aforementioned, we decided to explore the scope of CM reaction of β-arylated α-methylidene-β-lactams and selected terminal olefins with the aim to develop a new synthetic approach to Ezetimibe.

RESULTS AND DISCUSSION

At the outset we decided to study CM of 3-methylidene-1,4-diphenylazetidin-2-one **1a** with styrene **2a** as model substrates in the presence of the ruthenium-based Hoveyda−Grubbs second-generation catalyst[9] to assess the best reaction conditions (Table 1). Initially, the reaction was performed with **1a** and **2a** in 1:2 ratio under standard conditions at 40 °C either in dichloromethane (for 40 h) or in toluene (for 90 h) (entries 1 and 2). It provided the desired α-alkylidene-β-lactam **3aa** in identical yields of 29%. Higher yields of **3aa** were obtained when the reaction was carried out at 100 °C either in toluene (48%) or octafluorotoluene[10] (59%) (entries 3 and 4). Further screening of the reaction conditions showed that a portionwise addition of the catalyst had a beneficial effect on the yield of **3aa** (entries 5 and 6). The use of CuI as an additive, which has been shown to have a positive effect on the course of CM,[11] resulted in the drop of **3aa** yield (entries 7 and 8). Obviously, the use of a perfluorinated solvent (octafluorotoluene) had a positive effect on the course of the reaction.[8] It is also worth mentioning that in all cases the exclusive formation of the *Z*-isomer was observed.

During the course of our experiments, a paper describing effect of residual water, air, a catalyst load, etc. on the efficacy of

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Scheme 1. Retrosynthetic Analysis of Ezetimibe

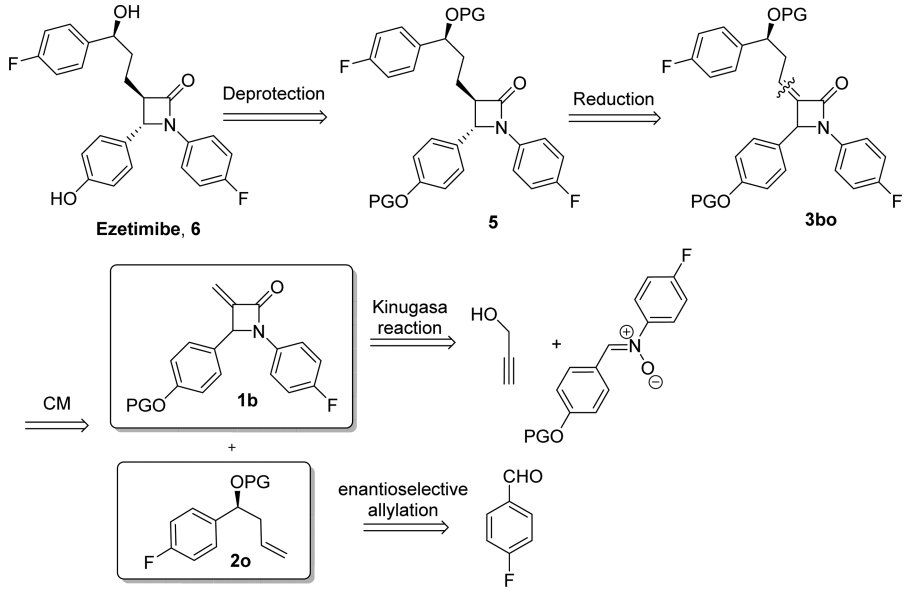
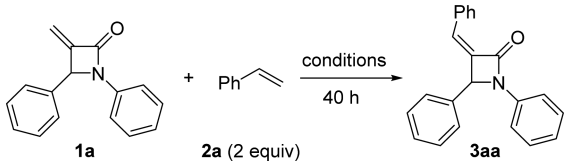


Table 1. CM between 1a and 2a under Various Conditions



entry	catalyst	cat. load (mol %)	solvent	T (°C)	yield (%)[a]
1	H-G II	10	dichloromethane	40	29
2[b]	H-G II	10	toluene	40	29
3	H-G II	10	toluene	100	48
4	H-G II	10	$C_6F_5CF_3$	100	51
5	H-G II	3 × 3[c]	toluene	100	58
6	H-G II	3 × 3[c]	$C_6F_5CF_3$	100	83
7[d]	H-G II	10	$C_6F_5CF_3$	100	48
8[d]	H-G II	3 × 3[c]	$C_6F_5CF_3$	100	74
9	H-G II	3 × 3[c]	toluene	100	77[e]
10	**H-G II**	**3 × 3[c]**	**$C_6F_5CF_3$**	**100**	**88[e]**
11	G I	3 × 3[c]	DCM	40	40[e]
12	G I	3 × 3[c]	$C_6F_5CF_3$	80	30[e]
13	G II	3 × 3[c]	$C_6F_5CF_3$	80	71[e]
14	H-G I	3 × 3[c]	$C_6F_5CF_3$	80	30[e]

[a]Isolated yields. [b]Reaction was stirred at given temperature for 90 h. [c]3 mol % of the catalyst was added in 3 portions during course of the reaction. [d]In the presence of CuI (15 mol %). [e]^{1}H NMR yields (mesitylene was used as the internal standard).

CM was published.[12] In view of these results, lactam **1a** was, prior to the reaction, evaporated several times with toluene to reduce its amount, and styrenes were distilled. Thus, a reaction of **1a** with **2a** carried out in toluene provided **3aa** in almost double yield of 77% (Table 1, entry 9) in comparison with undried substrates (entry 3). A similar effect albeit not so dramatic was observed also in octafluorotoluene (entry 10). These results thus clearly indicated that a reduction of an amount of residual water in reactants had beneficial effect on the reaction yields. In order to assess influence of a catalyst, reactions catalyzed by G I (entries 11 and 12), G II (entry 13), and H-G I (entry 14) were carried out. The reactions in octafluorotoluene were conducted at 80 °C to avoid decomposition of the catalysts used at higher temperatures. Although the desired product was obtained in all cases, only in the case of G II, a reasonable yield of 71% of **3aa** was achieved (entry 13). The use G I and H-G I provided **3aa** in 30−40% yields only (entries 11, 12, and 14). The above-mentioned results clearly indicate that suitable conditions for CM of **1a** with **2a** are as follows: a portion-wise addition of H-G II and the use octafluorotoluene as the solvent (entry 10).

With the optimized reaction conditions on hand, we proceeded with a study of CM reaction of β-arylated α-methylidene-β-lactams **1a** and **1b** with selected monosubstituted alkenes **2** in 1:2 ratio (Table 2). Initially, the metatheses of **1a** with several substituted styrenes **2b**−**2h** were carried out. A reaction with 4-nitrostyrene **2b** provided the corresponding **3ab** in a higher yield in toluene (66%) than in octafluorotoluene (51%) (entries 1 and 2). In a similar manner, reactions also proceeded with 4-cyanostyrene **2c**, 4-trifluoromethylstyrene **2d**, 4-chlorostyrene **2e**, 4-carboxymethylstyrene **2f**, and 4-acetoxystyrene **2g** furnishing the corresponding lactames **3ac**-**3ag** in good 41−83% isolated yields (entries 3−7). Surprisingly, the use of electron-rich styrene **2h** gave rise to 4,4′-dimethoxystilbene only (entry 8), and an attempt to carry out a reaction with 2-vinylnaphthalene **2i** resulted in the formation of a complex reaction mixture in which the desired product was not detected (entry 9). A significant drop in yields of metathesis products was observed in the reactions of **1a** with allylbenzene **2j**. In both solvents yields were 43% (entries 10 and 11). With respect to our goal, the reactivity of **1a** toward the unprotected **2k** and protected homoallylic alcohols **2l**−**2n** was also studied. Attempts to carry out CM of **1a** with **2k**−**2m** did not give rise to the desired CM products (entries 12−14). Gratifyingly, employing the TBDMS protected homoallylic alcohol **2n** led to the formation of the desired product **3an**. The nonreactivity of **2k**−**2m** could be speculatively explained by the formation of an internal interaction between the lone electron pair of the oxygen atom from the corresponding hydroxyl, acetate, or benzyloxy group with Ru-carbene complex.[13] The coordinatively saturated complex became unproductive in further transformation. Notably, lack of reaction of protected

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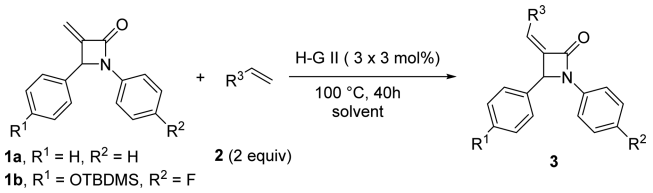
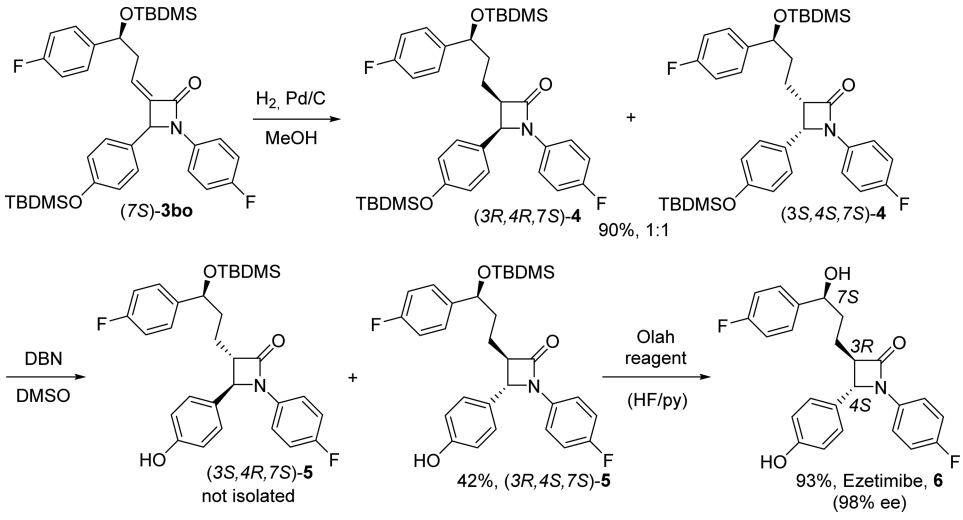
Table 2. CM of 1 with Various Alkenes 2a−2o



entry	1	2	R^3	solvent	3	yield (%)[a]
1	**1a**	**2b**	4-$O_2NC_6H_4$	toluene	**3ab**	66
2	**1a**	**2b**	4-$O_2NC_6H_4$	$C_6F_5CF_3$	**3ab**	51
3	**1a**	**2c**	4-NC-C_6H_4	$C_6F_5CF_3$	**3ac**	83
4	**1a**	**2d**	4-CF_3-C_6H_4	$C_6F_5CF_3$	**3ad**	62
5	**1a**	**2e**	4-Cl-C_6H_4	$C_6F_5CF_3$	**3ae**	41
6	**1a**	**2f**	4-MeOOC-C_6H_4	$C_6F_5CF_3$	**3af**	51
7	**1a**	**2g**	4-AcO-C_6H_4	$C_6F_5CF_3$	**3ag**	52
8	**1a**	**2h**	4-MeO-C_6H_4	$C_6F_5CF_3$	**3ah**	0[b]
9	**1a**	**2i**	2-naphthyl	$C_6F_5CF_3$	**3ai**	–[c]
10	**1a**	**2j**	$PhCH_2$	toluene	**3aj**	43
11	**1a**	**2j**	$PhCH_2$	$C_6F_5CF_3$	**3aj**	43
12	**1a**	**2k**	*rac*-PhCH(OH)CH_2	toluene or $C_6F_5CF_3$	**3ak**	0
13	**1a**	**2l**	*rac*-PhCH(OAc)CH_2	toluene or $C_6F_5CF_3$	**3al**	0
14	**1a**	**2m**	*rac*-PhCH(OBn)CH_2	toluene or $C_6F_5CF_3$	**3am**	0
15	**1a**	**2n**	*rac*-PhCH(OTBDMS)CH_2	toluene	**3an**	72
16	**1a**	**2n**	*rac*-PhCH(OTBDMS)CH_2	$C_6F_5CF_3$	**3an**	57
17	**1b**	(*S*)-**2o**	(*S*)-4-F-C_6H_4CH(OTBDMS)CH_2	toluene	(7*S*)-**3bo**	67
18[d]	(*R*)-**1b**	(*S*)-**2o**	(*S*)-4-F-C_6H_4CH(OTBDMS)CH_2	toluene	(4*R*,7*S*)-**3bo**	65

[a]Isolated yields. [b]4,4′-Dimethoxystilbene was formed. [c]A complex reaction mixture. [d]Compound **1b** with 72% ee of (*R*)- isomer.

Scheme 2. Synthesis of Ezetimibe (6) from (*S*)-3bo



homoallylic alcohols in similar situations has also been reported.[14] On the other hand, the bulky TBDMS group in **2n** and **2o** (entries 15−18) prevented the formation of this internally stabilized complex, and thus the reactions proceeded.[15] Nevertheless, successful CMs of homoallylic alcohols were reported as well,[16] and thus the lack of reactivity of **2k**−**2m** might be a complex issue. In order to compare, the solvent effect CM of **1a** with **2n** was carried out in toluene and octafluorotoluene (entries 15 and 16). Interestingly, as in the cases of **2b** (entries 1 and 2), a better yield of **3an** was obtained in toluene (72%) than in octafluorotoluene (57%). Although these results may seem rather puzzling, there is not currently any rational explanation for the observed solvent effect. Finally, CM metathesis of **1b** in toluene with (*S*)-**2o**, prepared either by allylation of 4-fluorobenzaldehyde with allyl boronate (98% ee)[6] or by allyltrichlorosilane (95% ee),[17] gave rise to (*S*)-**3bo** in a good 67% yield (entry 17). In all cases *Z*-stereoisomers were exclusively formed based on ^{1}H NMR. Formation of the corresponding *E*-isomers was not observed, and the structures of the *Z*-isomers were unequivocally confirmed by the X-ray diffraction analysis of **3aa** and **3aj**.[18] Our results are in agreement with observations described by Howell[8] and Ding.[23] An increased *Z*-selectivity in CM of **1** with **2** could be explained by lowered steric hindrance of bulkier phenyl, benzyl, and branched benzyl substituents of **2a**−**2o** and aryl moiety (Ph

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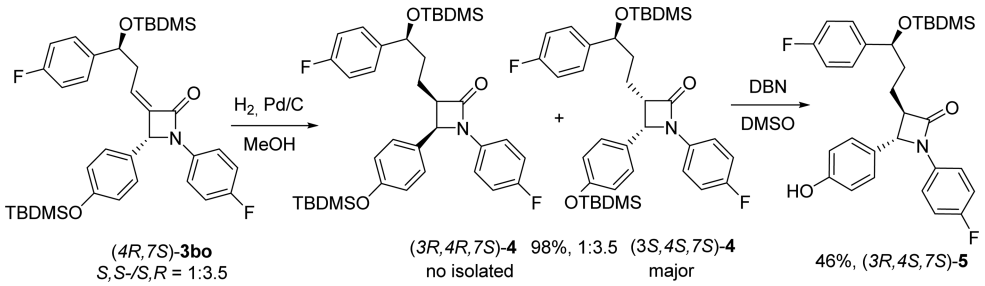
Scheme 3. Synthesis of (3*R*,4*S*,7*S*)-5 from (*S*,*S*)-3bo



or $TBDMSOC_6H_4$) at C-4 of **1a,b** in corresponding CM products **3** with *Z*-configuration.

In summary, despite the fact that octafluorotoluene seemed to be the solvent of choice, in some cases, performing reactions in toluene gave better results, indicating a complex relationship of influence of solvent effect on the course of the reaction.

With the above-described results on hand, we proceeded with the synthesis of Ezetimibe (**6**, Scheme 2). Having obtained (7*S*)-**3bo** in a good yield (67%), hydrogenation of the trisubstituted double bond by using Pd/C in MeOH ensued. The hydrogenation proceeded exclusively from the less hindered side, providing the corresponding *cis*-β-lactam **4** as 1:1 mixture of (3*R*,4*R*,7*S*)- and (3*S*,4*S*,7*S*)-diastereoisomers in 90% isolated yield. The exclusive preference for the formation of the *cis*-lactam is caused by steric hindrance exerted by the β-aryl substituent. Our observation is in agreement with results of hydrogenation of structurally similar α-alkylidene-β-lactams reported previously.[19,20] An attempt to employ other hydrogenation methods, such as the Stryker's reagent,[21] resulted in the formation of a rather complex reaction mixture out of which only a small amount (~30%) of the *cis*-products was isolated. In order to convert the *cis*-lactam **4** to the desired *trans*-lactam, epimerization by using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in DMSO was applied. During this process, not only epimerization at the position 3 occurred, but also deprotection of the phenolic hydroxyl group to the monosilylated *trans*-lactam **5** was observed. (3*R*,4*R*,7*S*)-Lactam **5** was easily isolated from the mixture of *trans*-diastereoisomers in 42% yield as a single enantiomer. Deprotection of the residual TBDMS group from the secondary alcohol moiety was accomplished by using Olah reagent (HF/pyridine)[22] in a mixture of THF/pyridine providing Ezetimibe in a high yield of 93% without loss of optical purity (98% ee), which was the same as that of the starting alcohol (*S*)-**2o** (98% ee).

This approach can be performed even more effectively when enantimerically enriched α-methylidene-β-lactam **1b** was used. Our attempt to prepare enantiomerically pure **1b** using asymmetric amination/lactamization reaction sequence[23] starting from the corresponding Morita–Baylis–Hillman acetate led to formation of (*R*)-**1b** in an acceptable yield (41%) but with 72% ee only. Although we duly followed the published procedure,[4b] we were not able to achieve the reported enantioselectivity of 95% ee. CM of (*R*)-**1b** with (*S*)-**2o** resulted in the formation of (4*R*,7*S*)-**3bo** as a mixture of diastereoisomers (*S*,*S*/*S*,*R* = 1:3.5). Subsequent hydrogenation of diastereomerically enriched (4*R*,7*S*)-**3bo** on Pd/C followed by DBN-based epimerization led to formation of (3*R*,4*S*,7*S*)-**5** in only slightly higher yield (46% from (4*R*,7*S*)-**3bo**) (Scheme 3). Lower yield of (3*R*,4*S*,7*S*)-**5** is probably caused by opening of the lactam ring. Based on the reported protocol, Ezetimibe (**6**) was prepared from the corresponding homoallylic alcohol and β-lactam in 4 steps and 30% overall yield.

CONCLUSION

In summary, we have explored the Ru-catalyzed CM reaction between β-arylated α-methylidene-β-lactams and selected olefins. The reaction was efficiently catalyzed by the Hoveyda–Grubbs second-generation catalyst furnishing the corresponding α-alkylidene-β-aryl-β-lactams in good yields and with the exclusive *Z*-selectivity. The developed protocol was successfully applied for enantioselective preparation of Ezetimibe (the commercial cholesterol absorption inhibitor) by using CM, reduction, epimerization, and desilylation reaction sequence in the overall yield of 30%.

EXPERIMENTAL SECTION

General Procedure for Preparation of (*Z*)-Nitrones. Following the reported procedure,[24] to a stirred solution of a nitrobenzene (100 mmol) in aqueous EtOH (50 mL, 50% aq.), ammonium chloride was added (6.25 g, 120 mmol). The resulting suspension was cooled to 0 °C by immersion to an ice bath then zinc dust (15.5 g, 240 mmol) was added in 5 portions, keeping the reaction temperature below 10 °C. The resulting gray suspension was stirred for 20 min, then a solution of a benzaldehyde (70 mmol) in AcOH (50 mL) was added, and the mixture was stirred another 30 min. The resulting crystalline mass was dissolved in toluene (200 mL). The organic phase was separated and washed with water (2 × 100 mL), aqueous saturated $NaHCO_3$ solution (100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to volume of 50 mL. Hexane (120 mL) was added, and the precipitated crystals were collected on a sintered glass funnel and washed with hexane (3 × 20 mL), and the pure product was dried under reduced pressure.

C,N-Diphenylnitrone. The reaction was carried out with nitrobenzene (12.50 g, 100 mmol) and benzaldehyde (7.43 g, 70 mmol). The title compound was obtained as a pale yellow solid (8.12 g, 57%). ^{1}H and ^{13}C NMR data were in agreement with the previously reported values.[25]

C-(4-t-Butyldimethylsilyloxyphenyl)-N-(4-fluorophenyl)nitrone. The reaction was carried out with 4-fluoronitrobenzene (7.41 g, 53 mmol) and 4-(*t*-butyldimethylsilyloxy)benzaldehyde (8.61 g, 37 mmol). The title compound was obtained as a pale yellow solid (4.75 g, 38%). Mp 117–119 °C (MeCN). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34–8.31 (m, 2H), 7.81–7.75 (m, 3H), 7.16–7.13 (m, 2H), 6.96–6.93 (m, 2H), 1.00 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.1, 157.9, 144. 8, 133.9, 130.7, 123.2, 119.9, 115.7, 115.4, 25.1, 17.8, −4.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.96 to (−110.87) (m); IR (KBr): 3120, 3049, 3016, 2959, 2947, 2929, 2890, 2857, 1906, 1691, 1595, 1509, 1497, 1473, 1422, 1320, 1284, 1254, 1236, 1195, 1069, 914, 839, 782 cm^{-1}; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{25}FNO_2Si$ 346.1633; found 346.1632

General Procedure for Preparation of 3-Methylenelactames (1). Following the reported procedure,[5] DMSO (6 mL) was added to (*S*)-proline (173 mg, 1.5 mmol) under argon, then propargyl alcohol (84 mg, 1.5 mmol) was added, and the suspension was stirred 30 min.

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Then CuI (286 mg, 1.5 mmol) was added in a stream of argon, and the resulting yellow-green suspension was stirred for 5 min. After that, a solution of a nitrone (1.5 mmol) in DMSO (6 mL) was added in a stream of argon, and the reaction mixture was stirred for 18 h. It was then poured into dichloromethane (50 mL) and water (50 mL), vigorously mixed, and then the mixture was filtered through a short column of silica gel (10 g) on a sintered funnel. The column was washed with dichloromethane (5 × 10 mL), the biphasic filtrate was transported to a separating funnel, and the organic phase separated. The water phase was extracted with dichloromethane (3 × 10 mL), and the combined organic phases were washed with water (5 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexane → 5/1 hexane-EtOAc) furnished the title compound.

*3-Methylene-1,4-diphenylazetidin-2-one (**1a**).* The reaction was carried out with diphenylnitrone (3.00 g, 15 mmol). Column chromatography furnished 0.677 g (19%) of the title compound as a pale yellow crystals. ^{1}H and ^{13}C NMR data were in agreement with the reported values.[5]

*4-[4-(t-Butyldimethylsilyloxy]phenyl]-1-(4-fluorophenyl)-3-methyleneazetidin-2-one (**1b**).* The reaction was carried out with the corresponding nitrone (520 mg, 1.5 mmol). Column chromatography furnished 90 mg (16%) of the title compound as a colorless solid. Mp 112−114 °C (MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32−7.30 (m, 2H), 7.24−7.23 (m, 2H), 6.96−6.93 (m, 2H), 6.84−6.82 (m, 2H), 5.83 (t, J = 1.8 Hz, 1H), 5.32 (s, 1H), 5.16 (s, 1H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.9, 159.9, 158.3, 156.2, 150.0, 133.9, 128.5, 128.0, 120.6, 118.5, 115.9, 115.6, 110.9, 63.5, 25.6, 18.1, −4.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.63 to −117.72 (m); IR (KBr): 3091, 3078, 3062, 3033, 2953, 2931, 2883, 2857, 1739, 1607, 1509, 1470, 1374, 1266, 1227, 1126, 911, 836, 809 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{22}H_{26}FNNaO_2Si$ 406.1609; found 406.1609.

*(S)-[1-(4-Fluorophenyl)but-3-en-1-yloxy](t-butyl)dimethylsilane ((S)-**2o**).* Following the reported procedure,[26] *t*-butyl(dimethyl)silyl chloride (720 mg, 4.79 mmol) was added to a solution of (*S*)-[1-(4-fluorophenyl)but-3-en-1-ol[6] (551 mg, 3.31 mmol) and imidazole (407 mg, 5.97 mmol) in DMF (6.0 mL), and the resulting reaction mixture was stirred for 4 h. Then it was poured to a mixture of dichloromethane (10 mL) and water (10 mL). The phases were separated, the aqueous phase was extracted with dichloromethane (10 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl solution (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexane, 20 g) furnished 710 mg (75%) of the title compound as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30−7.27 (m, 2H), 7.02−6.99 (m, 2H), 5.80−5.75 (m, 1H), 5.04 (s, 1H), 5.02−5.01 (m, 1H), 4.69 (t, J = 5.4 Hz, 1H) 2.49−2.35 (m, 2H), 0.91 (s, 9H), 0.06 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.6, 161.0, 140.9, 134.9, 127.4, 117.1, 114.8, 74.3, 45.5, 25.8, 18.2, −4.7, −5.0; ^{19}F NMR (282 MHz) δ −116.09 to −115.99 (m); $[\alpha]_D$ = −40.5° (c = 0.237, $CHCl_3$); IR (KBr): 3072, 2959, 2926, 2896, 2857, 1882, 1829, 1760, 1643, 1607, 1509, 1467, 1632, 1251, 1227, 1153, 1081, 1003, 914, 836, 776 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{26}FOSi$ 281.1732; found 281.1736.

General Procedure for CM of Lactams 1 with Alkenes 2. Method A. (Catalyst loading in one portion): In a vial with a PTFE septum (4 mL) was dissolved lactam **1** (0.1 mmol) under argon in a dry solvent (1 mL), then alkene **2** (0.2 mmol) and the Hoveyda−Grubbs second-generation catalyst (6.2 mg, 0.01 mmol) were added, and the reaction mixture was stirred at given temperature for given time. Then the mixture was concentrated under reduced pressure and column chromatography of the residue on silica gel (toluene) furnished the desired product **3**.

General Procedure for CM of Lactams 1 with Alkenes 2. Method B. (Gradual catalyst loading): In a vial with a PTFE septum (4 mL) was dissolved lactam **1** (0.1 mmol) under argon in a dry solvent (1 mL), then alkene **2** (0.2 mmol) and the Hoveyda−Grubbs second-generation catalyst (1.9 mg, 0.003 mmol) were added, and the reaction mixture was stirred at 100 °C for 12 h. Then the second portion of Hoveyda−Grubbs second-generation catalyst (1.9 mg, 0.003 mmol) was added, and the mixture was stirred again at 100 °C. After 12 h the final portion of the catalyst (1.9 mg, 0.003 mmol) was added, and the stirring of the reaction mixture at 100 °C continued for 16 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and column chromatography of the residue on silica gel (toluene) furnished the desired product **3**.

*(Z)-3-Benzyliden-1,4-diphenylazetidin-2-one (**3aa**).* The reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2a** (21 mg, 0.20 mmol). Column chromatography furnished **3aa** (method A, 16.0 mg, 51%; method B, 26 mg, 83%) as a colorless crystalline solid. The compound was recrystallized from methanol/acetone mixture (2/1) for X-ray structure analysis. NMR data were in agreement with the reported values.[27]

*(Z)-3-(4-Nitrobenzylidene)-1,4-diphenylazetidin-2-one (**3ab**).* According method B of the general procedure, the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2b** (30 mg, 0.20 mmol). Column chromatography furnished 23 mg (66%) of the title compound as yellow needles. NMR data were in agreement with the reported values.[28]

*(Z)-1,4-Diphenyl-3-(4-cyanobenzylidene)azetidin-2-one (**3ac**).* Following the general procedure (method B), the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2c** (0.026 mL, 0.20 mmol). Column chromatography (4/1 hexanes/EtOAc) funished **3ac** 28 mg (83%) as a yellow solid. Mp 215−218 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12−8.10 (m, 2H), 7.68−7.66 (m, 2H), 7.45−7.38 (m, 7H), 7.31−7.28 (m, 2H), 7.11−7.08 (m, 1H), 6.28 (s, 1H), 5.44 (d, J = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.5, 144.3, 138.0, 137.4, 136.3, 132.4, 130.3, 129.3, 129.2, 129.1, 128.5, 126.7, 124.6, 118.7, 117.2, 112.5, 62.4; IR (KBr): 2926, 2226, 1721, 1709, 1503, 1494, 1377, 1135, 755 cm^{-1}; HRMS (TOF-MS-CI) m/z: [M + H]$^+$ Calcd for $C_{23}H_{17}N_2O$ 337.1335; found 337.1340.

*(Z)-1,4-Diphenyl-3-(4-(trifluoromethyl)benzylidene)azetidin-2-one (**3ad**).* Following the general procedure (method B), the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2d** (0.030 mL, 0.20 mmol). Column chromatography (4/1 hexanes/EtOAc) funished **3ad** 23.5 mg (62%) as a colorless solid. Mp 226−227.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12−8.11 (m, 2H), 7.64−7.63 (m, 2H), 7.46−7.38 (m, 7H), 7.31−7.28 (m, 2H), 7.10−7.07 (m, 1H), 6.31 (s, 1H), 5.43 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.8, 143.2, 137.6, 137.1, 136.5, 130.90 (q, J = 32.62 Hz), 130.1, 129.3, 129.2, 129.0, 128.9, 126.7, 125.6 (q, J = 3.78 Hz), 124.36, 124.0 (q, J = 272.40 Hz), 117.10, 62.34; ^{19}F NMR (400 MHz, $CDCl_3$) δ −62.9; IR (KBr) 1724, 1503, 1386, 1326, 1168, 1132, 1123, 1069 cm^{-1}; HRMS (TOF-MS-CI) m/z: [M + H]$^+$ Calcd for $C_{23}H_{17}F_3NO$ 380.1250; found 380.1256.

*(Z)-1,4-Diphenyl-3-(4-chlorobenzylidene)azetidin-2-one (**3ae**).* Following the general procedure (method B), the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2e** (0.023 mL, 0.20 mmol). Column chromatography (4/1 hexanes/EtOAc) funished **3ae** 14 mg (41%) as a colorless solid. Mp 253−255 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96−7.94 (m, 2H), 7.45−7.34 (m, 9H), 7.30−7.27 (m, 2H), 7.08−7.05 (m, 1H), 6.23 (s, 1H), 5.40 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.1, 141.1, 137.7, 136.8, 135.5, 132.5, 131.3, 129.5, 129.2, 129.1, 128.9, 128.8, 126.7, 124.2, 117.0, 62.3; IR (KBr) 1715, 1589, 1494, 1452, 1374, 1350, 1132, 839, 749 cm^{-1}; HRMS (TOF-MS-CI) m/z: [M + H]$^+$ Calcd for $C_{22}H_{17}ClNO$ 346.0993; found 346.1000.

*Methyl (Z)-4-((2-Oxo-1,4-diphenylazetidin-3-ylidene)methyl)-benzoate (**3af**).* Following the general procedure (method B), the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2f** (0.031 g, 0.20 mmol). Column chromatography (4/1 hexanes/EtOAc) funished **3af** 18.5 mg (51%) as a colorless solid. Mp 188−190 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07−8.04 (m, 4H), 7.45−7.37 (m, 7H), 7.30−7.27 (m, 2H), 7.09−7.06 (m, 1H), 6.31 (d, J = 1.2 Hz, 1H), 5.42 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 159.8, 143.0, 138.5, 137.6, 136.6, 130.5, 130.1, 129.8 (d, J = 4.08 Hz), 129.5, 129.2 (d, J = 5.29 Hz), 128.9, 126.7, 126.6, 124.3, 117.1, 62.3, 52.2; IR (KBr) 1724, 1595, 1503, 1434, 1377, 1344, 1284, 1105, 908, 752 cm^{-1}; HRMS (TOF-MS-CI) m/z: [M + H]$^+$ Calcd for $C_{24}H_{20}NO_3$ 370.1438; found 370.1436.

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J. Org. Chem. 2016, 81, 7692−7699

*(Z)-4-((2-Oxo-1,4-diphenylazetidin-3-ylidene)methyl)phenyl acetate (**3ag**).* Following the general procedure (method B), the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2g** (0.030 mL, 0.20 mmol). Column chromatography (4/1 hexanes/EtOAc) funished **3ag** 19 mg (52%) as a colorless solid. Mp 184−186 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05−8.03 (m, 2H), 7.45−7.43 (m, 2H), 7.41−7.39 (m, 4H), 7.37−7.34 (m, 1H), 7.29−7.26 (m, 2H), 7.13−7.10 (m, 2H), 7.07−7.05 (m, 1H), 6.26 (s, 1H), 5.40 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.2, 160.3, 151.5, 140.6, 137.8, 136.9, 131.8, 131.3, 129.8, 129.2, 129.1, 128.8, 126.8, 124.1, 121.8, 117.0, 62.2, 21.1; IR (KBr) 3069, 3025, 2361, 2325, 1763, 1715, 1601, 1506, 1497, 1452, 1374, 1210, 1165, 1135, 1009, 917, 851, 752 cm^{-1}; HRMS (TOF-MS-CI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}NO_3$ 370.1432; found 370.1430.

*(Z)-1,4-Diphenyl-3-(2-phenylethyliden)azetidin-2-one (**3aj**).* Following the general procedure (method B), the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2j** (23.6 mg, 0.20 mmol). Column chromatography furnished 14 mg (43%) of the title compound as a colorless solid. The compound was recrystallized from methanol for X-ray structure analysis. Mp 143−145 °C (MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40−7.20 (m, 14 H), 7.07−7.04 (m, 1H), 5.74 (t, J = 6.3 Hz, 1 H), 5.35 (s, 1 H), 4.05−4.01 (m, 1 H), 3.81−3.77 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.6, 141.6, 138.9, 137.8, 137.0, 130.1, 129.1, 129.0, 128.7, 128.6, 128.5, 126.5, 123.8, 116.9, 62.8, 34.9; IR (KBr): 3060, 3028, 2929, 1727, 1589, 1500, 1455, 1374, 1129, 749, 701 cm^{-1}; HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{23}H_{19}NO$ 325.1467; found 325.1463.

*(Z)-3-(3-(t-Butyldimethylsilyloxy)-3-phenylpropyliden-1,4-diphenylazetidin-2-one (**3an**).* According method B of the general procedure, the reaction was carried out with **1a** (23 mg, 0.10 mmol) and **2n** (53 mg, 0.20 mmol). Column chromatography furnished 34 mg (72%) of the title compound as 1/1 mixture of diastereoisomers as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.20 (m, 28H), 7.03−7.01 (m, 2H), 5.62 (t, J = 7.5 Hz, 2H), 5.27 (d, J = 3 Hz, 2H), 4.85 (t, J = 6 Hz, 1H), 4.73 (m, 1H), 3.02−2.81 (m, 4H), 0.85 (s, 9H), 0.80 (s, 9H), −0.01 (s, 3H), −0.13 (s, 3H), −0.15 (s, 3H), - 0.20 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.5, 144.2, 144.1, 142.7, 142.6, 137.9, 137.0, 129.1, 129.0, 128.9, 128.5, 128.4, 128.1, 128.0, 127.1, 127.0, 126.6, 126.5, 125.8, 125.7, 123.7, 116.9, 74.5, 74.3, 62.8, 39.5, 39.3, 25.8, 25.7, 18.1, −4.8, −5.0, −5.3 ppm; IR (KBr): 3084, 3060, 3031, 2956, 2935, 2896, 2854, 1751, 1595, 1500, 1455, 1371, 1254, 1120, 1090, 1066, 937, 839, 779, 755, 698 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{36}NO_2Si$ 470.2510; found 470.2502.

*3′-(S)-4-(R,S)-(Z)-3-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)propylid-1-en]-4-(4-t-butyldimethylsilyloxy)phenyl-1-(4-fluorophenyl)azetidin-2-one ((7S)-**3bo**).* According method B of the general procedure, the reaction was carried out with **1b** (67 mg, 0.175 mmol) and (*S*)-**2o** (98 mg, 0.35 mmol). Column chromatography furnished 75 mg (67%) of the title compound as 1/1 mixture of diastereoisomers as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27−6.78 (m, 24H), 5.58 (t, J = 7.5 Hz, 2H), 5.18 (d, J = 7.7 Hz, 2H), 4.84 (t, J = 6 Hz, 1H), 4.72 (m, 1H), 3.04−2.74 (m, 4H), 0.98 (s, 9H), 0.97 (s, 9H), 0.85 (s, 9H), 0.80 (s, 9H), 0.20 (dd, J = 1.7, 3.2 Hz, 12H), −0.00 (s, 3H), −0.12 (d, J = 4.5 Hz, 6 H), −0.19 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7, 162.6, 161.3, 161.3, 161.1, 161.0, 159.7, 158.1, 156.0, 143.2, 143.1, 140.0, 139.8, 134.2, 129.2, 129.1, 127.9, 127.8, 127.4, 127.3, 127.2, 127.1, 120.5, 120.4, 118.2, 115.9, 115.7, 115.0, 114.9, 114.8, 114.7, 73.9, 73.6, 62.7, 39.5, 39.2, 25.7, 25.7, 25.6, 18.2, 18.1, 18.0, −4.4, −4.9, −5.0, −5.2; ^{19}F NMR (282 MHz) δ −115.67 to −115.79 (m, 1F), −115.92 to −116.10 (m, 1F), −118.12 to −118.43 (m, 2F); $[\alpha]_D$ = 0 (c = 0.096, $CHCl_3$); IR (KBr): 2956, 2935, 2881, 2857, 1751, 1604, 1512, 1473, 1380, 1278, 1263, 1227, 1174, 1135, 917, 839, 782 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{48}F_2NO_3Si_2$ 636.3135; found 636.3137.

*3′-(S)-4-(R,S)-(Z)-3-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)propylid-1-en]-4-(4-t-butyldimethylsilyloxy)phenyl-1-(4-fluorophenyl)azetidin-2-one ((4R,7S)-**3bo**).* According method B of the general procedure, the reaction was carried out with (*R*)-**1b** (34.7 mg, 0.09 mmol) and (*S*)-**2o** (50.7 mg, 0.18 mmol). Column chromatography furnished 37 mg (65%) of the title compound as 1/3.5 mixture of diastereoisomers (4*R*,7*S* major/4*S*,7*S* minor) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27−6.79 (m, 12.33H), 5.58 (t, J = 7.4 Hz, 1H), 5.18 (d, J = 7.8 Hz, 1H), 4.85 (dd, J = 6 Hz, 5.2 Hz, 0.80H, 4*R*,7*S*), 4.73 (dd, J = 7.2 Hz, 5.0 Hz, 0.23H, 4*S*,7*S*), 3.04−2.95 (m, 0.99H), 2.88−2.84 (m, 0.81H, 4*R*,7*S*), 2.79−2.75 (m, 0.22H, 4*S*,7*S*), 0.98 (d, 8.50H), 0.85 (s, 7.05H, 4*R*,7*S*), 0.80 (s, 1.68H, 4*S*,7*S*), 0.20 (dd, J = 4.9, 1.7 Hz, 5.64H), −0.00 (s, 2.37H, 4*R*,7*S*), −0.12 (d, J = 4.3 Hz, 2.86 H), −0.18 (s, 0.53H, 4*S*,7*S*); ^{13}C NMR (151 MHz, CDCl3) δ 162.73, 162.65, 161.34, 161.32, 161.11, 161.03, 159.73, 158.12, 156.04, 143.20, 143.13, 140.03, 140.01, 139.82, 139.80, 134.17, 134.15, 129.17, 129.12, 127.95, 127.91, 127.88, 127.86, 127.36, 127.31, 127.25, 127.20, 120.49, 120.43, 118.23, 118.21, 118.18, 118.15, 115.85, 115.70, 115.00, 114.94, 114.86, 114.80, 73.92, 73.60, 62.75, 62.70, 39.50, 39.24, 25.75, 25.68, 25.60, 18.16, 18.14, 18.08, −4.42, −4.85, −5.01, −5.18; ^{19}F NMR (376 MHz) δ −115.67 to −115.75 (m, 0.18F, 4*S*,7*S*), −115.90 to −115.96 (m, 0.78F), −118.19 to −118.28 (m, 1F); $[\alpha]_D$ = −4.2 (c = 0.176, $CHCl_3$); IR (KBr): 2956, 2935, 2881, 2857, 1751, 1604, 1512, 1473, 1380, 1278, 1263, 1227, 1174, 1135, 917, 839, 782 cm^{-1}; HRMS (ESI-TOF) m/z: HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{48}F_2NO_3Si_2$ 636.3135; found 636.3139.

*3′-(S)-4-(R)-3-(R)-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)-propyl]-4-(4-t-butyldimethylsilyloxy)phenyl-1-(4-fluorophenyl)-azetidin-2-one (3R,4R,7S)-4 and 3′-(S)-4-(S)-3-(S)-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)propyl]-4-(4-t-butyldimethylsilyloxy)-phenyl-1-(4-fluorophenyl)azetidin-2-one, (3S,4S,7S)-**4**.* To a solution of **3bo** (20 mg, 0.03 mmol) in MeOH (2 mL) Pd/C (10%, 10 mg) was added and the flask was flushed with hydrogen. After 24 h of stirring under hydrogen atmosphere, the content of the flask was concentrated under reduced pressure, and column chromatography of the residue on silica gel (toluene, 10 g) furnished 18 mg (90%) of 1/1 mixture of diastereoisomers as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26−6.78 (m, 24H), 5.07−5.06 (m, 2H), 4.44−4.42 (m, 1H), 4.33−4.30 (m, 1H), 3.49−3.32 (m, 2H), 1.72−1.59 (m, 2H), 1.45−1.23 (m, 6H), 1.00 (s, 9H), 0.99 (s, 9H), 0.80 (s, 9H), 0.77 (s, 9H), 0.22 (s, 12H), −0.11 (s, 3H), −0.15 (s, 3H), −0.25 (s, 3H), −0.26 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.8, 167.6, 162.5, 160.9, 159.6, 158.0, 155.7, 140.8, 133.9, 128.2, 128.1, 127.1, 120.2, 120.1, 118.5, 118.4, 115.8, 115.6, 114.8, 114.7, 74.2, 73.9, 58.0, 54.7, 54.6, 38.2, 38.1, 25.7 (2×), 25.6, 22.0, 18.0, −4.4, −4.8, −5.1, −5.2 ; ^{19}F NMR (282 MHz) δ −116.01 to −116.11 (m, 1F), −116.19 to −116.29 (m, 1F), −118.38 to −118.51 (m, 2F); $[\alpha]_D$ = −13.9 (c = 0.200, $CHCl_3$); IR (KBr): 2956, 2926, 2899, 2857, 1721, 1709, 1559, 1535, 1512, 1263, 1222, 1099, 1087, 917, 836, 779 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{36}H_{49}F_2NNaO_3Si_2$ 660.3111; found 660.3112.

*3′-(S)-4-(R)-3-(R)-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)-propyl]-4-(4-t-butyldimethylsilyloxy)phenyl-1-(4-fluorophenyl)-azetidin-2-one (3R,4R,7S)-**5** and 3′-(S)-4-(S)-3-(S)-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)propyl]-4-(4-t-butyldimethylsilyloxy)-phenyl-1-(4-fluorophenyl)azetidin-2-one, (3S,4S,7S)-**5**.* To a solution of ((4*R*,7*S*)-**3bo**) (18 mg, 0.027 mmol) in MeOH (2 mL) Pd/C (10%, 8.5 mg) was added, and the flask was flushed with hydrogen. After 30 min of stirring under hydrogen atmosphere, the content of the flask was filtred through Celite and washed by (3 × 5 mL) of toluene. The procedure furnished 17.7 mg (98%) of 1/3.57 mixture of diastereoisomers (3*S*,4*S*,7*S* major; 3*R*,4*R*,7*S* minor) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26−6.78 (m, 12.19H), 5.07−5.06 (t, 1H), 4.43 (t, J = 5.6 Hz, 0.23H, 3*R*,4*R*,7*S*), 4.32 (dd, J = 7.5, 5.1 Hz, 0.80H, 3*S*,4*S*,7*S*), 3.49−3.42 (m, 0.98H), 1.73−1.58 (m, 2.51H), 1.45−1.26 (m, 2.61H), 1.13−1.05 (m, 0.90H) 1.00 (s, 8.63H), 0.90−0.84 (m, 0.79H), 0.79 (d, 8.34, 8.44H), 0.22 (s, 5.74H, 3*S*,4*S*,7*S*), −0.13 (d, J = 20.3 Hz, 2.92H), −0.25 (s, 3H), −0.26 (s, 2.80H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.76, 167.59, 162.55, 160.93, 159.64, 158.03, 155.78, 140.81, 140.79, 133.93, 133.91, 133.89, 128.25, 128.15, 127.18, 127.13, 127.10, 127.05, 126.83, 120.20, 120.17, 118.49, 118.44, 115.78, 115.63, 114.83, 114.69, 74.19, 73.92, 58.05, 58.03, 54.68, 54.60, 38.25, 38.20, 25.75, 25.72, 25.60, 22.01, 18.16, 18.13, 18.06, −4.40, −4.43, −4.77, −4.80, −5.09, −5. 19F NMR ^{19}F NMR (282 MHz, cdcl$_3$) δ −116.09 to −116.28 (m, 1F), −118.45 (dq, J = 8.4, 4.7 Hz, 1F); $[\alpha]_D$ = −44 (c = 0.187, $CHCl_3$); IR (KBr): 2956, 2926, 2899, 2857, 1721, 1709, 1559, 1535, 1512, 1263, 1222, 1099, 1087, 917, 836, 779 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{36}H_{49}F_2NNaO_3Si_2$ 660.3111; found 660.3108.

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J. Org. Chem. 2016, 81, 7692−7699

*3′-(S)-4-(S)-3-(R)-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)-propyl]-4-(4-hydroxyphenyl-1-(4-fluorophenyl)azetidin-2-one ((3R,4S,7S)-**5**).* To a solution of (3*S*,4*S*,7*S*)-**5**/(3*R*,4*R*,7*S*)-**5**, in a ratio of 1/1, (75 mg, 0.12 mmol) in DMSO (10 mL), 1,5-diazabicyclo[4.3.0]-non-5-ene (17 mg, 0.14 mmol) was added. After 24 h of stirring, the content of the flask was poured into aqueous hydrochloric acid (20 mL, 0.1 M) with stirring. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with water and dried with Na_2SO_4. The solution was concentrated under reduced pressure and column chromatography of the residue on silica gel (toluene-EtOAc 10/1, 25 g) and furnished 26 mg (42%) of the title compound as an colorless oil. Sample for characterization purposes was purified via reverse-phase preparative TLC. ^{1}H and ^{13}C NMR data were in agreement with the reported values.[29] ^{19}F NMR (282 MHz) δ −115.73 to −115.86 (m, 1F), −118.14 to −118.29 (m, 1F). $[\alpha]_D$ = −20.3 (*c* = 0.958, $CHCl_3$); LRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{30}H_{35}F_2NNaO_3Si$ 546.2; found 546.2.

*3′-(S)-4-(S)-3-(R)-[3′-t-Butyldimethylsilyloxy-3′-(4-fluorophenyl)-propyl]-4-(4-hydroxyphenyl-1-(4-fluorophenyl)azetidin-2-one ((3R,4S,7S)-**5**).* To a solution of (3*S*,4*S*,7*S*)-**5**/(3*R*,4*R*,7*S*)-**5** in a ratio of 3.5/1 (30 mg, 0.048 mmol) in DMSO (4 mL), 1,5-diazabicyclo[4.3.0]-non-5-ene (7 mg, 0.056 mmol) was added. After 13 h of stirring, the content of the flask was added dropwise to aqueous hydrochloric acid (8 mL, 0.1 M) with stirring. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with water and dried with Na_2SO_4. The solution was concentrated under reduced pressure and column chromatography of the residue on silica gel (EtOAc-Hexanes 7/1, 10 g); second column chromatography (EtOAc-Hexanes 10/1, 8 g) furnished 11.5 mg (46%) of the title compound as an colorless oil. ^{1}H and ^{13}C NMR data were in agreement with the reported values.[29] ^{19}F NMR (282 MHz) δ −115.73 to −115.86 (m, 1F), −118.14 to −118.29 (m, 1F). $[\alpha]_D$ = −20.3 (*c* = 0.958, $CHCl_3$); LRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{30}H_{35}F_2NNaO_3Si$ 546.2; found 546.2.

*3′-(S)-4-(S)-3-(R)-[3′-Hydroxy-3′-(4-fluorophenyl)propyl]-4-(4-hydroxyphenyl-1-(4-fluorophenyl)azetidin-2-one), Ezetimibe (**6**).* To a solution of (*S*,*R*,*S*)-**5** (20 mg, 0.04 mmol) in dry THF (1 mL), anhydrous pyridine (0.5 mL) was added, followed by HF·pyridine complex (0.5 mL). After 24 h of stirring at room temperature, aqueous sodium hydrogen carbonate (5 mL) was added with stirring. The mixture was extracted with EtOAc (4 × 5 mL), and the combined organic phases were washed with water and dried with Na_2SO_4. The content of the flask was concentrated under reduced pressure and flash chromatography of the residue on silica gel (chloroform → acetone, 10 g) furnished 15 mg (93%) of the title compound as a white solid. ^{1}H and ^{13}C NMR data were in agreement with the reported values.[29] ^{19}F NMR (282 MHz) δ −114.72 to −115.80 (m, 1F), −117.62 to −117.73 (m, 1F). $[\alpha]_D$ = −29.9 (*c* = 0.194, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01406.

^{1}H NMR spectra of **1a**, **1b**, **2n**, (*S*)-**2o**, **3aa**, **3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ag**, **3aj**, **3an**, (7*S*)-**3bo**, (4*R*,7*S*)-**3bo**, (3*R*,4*R*,7*S*)-**4**/(3*S*,4*S*,7*S*)-**4**, (3*R*,4*R*,7*S*)-**5**, Ezetimibe. ^{13}C NMR spectra of **1a**, **1b**, (*S*)-**2o**, **3ac**, **3ad**, **3ae**, **3af**, **3ag**, **3an**, (7*S*)-**3bo**, (4*R*,7*S*)-**3bo**, (3*R*,4*R*,7*S*)-**4**/(3*S*,4*S*,7*S*)-**4**, (3*R*,4*R*,7*S*)-**5**, Ezetimibe. ^{19}F NMR spectra of **1b**, (*S*)-**2h**, **3ad**, (7*S*)-**3bo**, (4*R*,7*S*)-**3bo**, (3*R*,4*R*,7*S*)-**4**/(3*S*,4*S*,7*S*)-**4**, (3*R*,4*R*,7*S*)-**5**, Ezetimibe. X-ray crystallographic data for **3aa** and **3aj** (PDF)

Crystallographic data (CIF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews on the biological activity of lactams, see: (a) Arya, N.; Jagdale, A. Y.; Patil, T. A.; Yeramwar, S. S.; Holikatti, S. S.; Dwivedi, J.; Shishoo, C. J.; Jain, K. S. *Eur. J. Med. Chem.* **2014**, *74*, 619−656. (b) Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. *Eur. J. Med. Chem.* **2010**, *45*, 5541−5560. (c) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072−5129.

(2) For selected reviews on β-lactams used as valuable synthetic intermediates, see: (a) Alcaide, B.; Almendros, P. *Chem. Record* **2011**, *11*, 311−330. (b) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2011**, *67*, 1989−2012. (c) Palomo, C.; Oiarbide, M. *Top. Heterocycl. Chem.* **2010**, *22*, 211−259. (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437−4492. (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Synthesis of β-Amino Acids and their Derivatives from β-Lactams: Update. In *Enantioselective Synthesis of β-amino acids*; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley & Sons: Hoboken, NJ, 2005 and references cited therein.

(3) (a) Sánchez, C. C.; Dobarro, R. A.; Bosch, C. J.; García, D. D. Patent WO2012004382A1, January 12, 2012. (b) Sasikala, C. H. V. A.; Padi, P. R.; Sunkara, V.; Ramayya, P.; Dubey, P. K.; Uppala, V. B. R.; Praveen, C. *Org. Process Res. Dev.* **2009**, *13*, 907−910. (c) Rosenblum, S. B. Advance in the Development of Methods for the Synthesis of Cholesterol Absorption Inhibitors: Ezetimibe. In *The Art of Drug Synthesis*; Johnson, D. S., Li, J. J., Eds.; Wiley-Intersience: Hoboken, NJ, 2007. (d) Clader, J. W. *J. Med. Chem.* **2004**, *47*, 1−9. (e) Wu, G.; Wong, Y.; Chen, X.; Ding, Z. *J. Org. Chem.* **1999**, *64*, 3714−3718. (f) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973−980. (g) Burnett, D. A.; Caplen, M. A.; Davis, H. R., Jr.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733−1736.

(4) For recent examples of Ezetimibe synthesis, see: (a) Śnieżek, M.; Stecko, S.; Panfil, I.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2013**, *78*, 7048−7057. (b) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y.-J.; Liu, L.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9276−9282. (c) Michalak, M.; Stodulski, M.; Stecko, S.; Mames, A.; Panfil, I.; Soluch, M.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2011**, *76*, 6931−6936. (d) Sova, M.; Mravljak, J.; Kovač, A.; Pečar, S.; Časar, Z.; Gobec, S. *Synthesis* **2010**, *2010*, 3433−3438. (e) Mothana, S.; Grassot, J.-M.; Hall, D. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 2883−2887. (f) Kyslíková, E.; Babiak, P.; Marešová, H.; Palyzová, A.; Hájíček, J.; Kyslík, P. *J. Mol. Catal. B: Enzym.* **2010**, *67*, 266−270. (g) Bertrand, B.; Durassier, S.; Frein, S.; Burgos, A. *Tetrahedron Lett.* **2007**, *48*, 2123−2125.

(5) Basak, A.; Ghosh, S. C. *Synlett* **2004**, *9*, 1637−1639.

(6) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884−11886.

DOI: 10.1021/acs.joc.6b01406
J. Org. Chem. 2016, 81, 7692−7699

(7) For selected reviews, see: (a) Donohoe, T. J.; Bower, J. F.; Chan, L. K. M. *Org. Biomol. Chem.* **2012**, *10*, 1322−1328. (b) Prunet, J. *Eur. J. Org. Chem.* **2011**, *2011*, 3634−3647. (c) Prunet, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1559−1577. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.
(8) Liang, Y.; Raju, R.; Le, T.; Taylor, C. D.; Howell, A. R. *Tetrahedron Lett.* **2009**, *50*, 1020−1022.
(9) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746−1787.
(10) For a beneficial effect of fluorinated solvents on the course of metathesis reactions, see: (a) Samojłowicz, C.; Borré, E.; Mauduit, M.; Grela, K. *Adv. Synth. Catal.* **2011**, *353*, 1993−2002. (b) Samojłowicz, C.; Bieniek, M.; Pazio, A.; Makal, A.; Woźniak, K.; Poater, A.; Cavallo, L.; Wójcik, J.; Zdanowski, K.; Grela, K. *Chem. - Eur. J.* **2011**, *17*, 12981−12993. (c) Samojlowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. *Chem. Commun.* **2008**, 6282−6284. (d) Rost, D.; Porta, M.; Gessler, S.; Blechert, S. *Tetrahedron Lett.* **2008**, *49*, 5968−5971.
(11) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697−4702.
(12) Guidone, S.; Songis, O.; Nahra, F.; Cazin, C. S. J. *ACS Catal.* **2015**, *5*, 2697−2701.
(13) McNaughton, B. R.; Bucholtz, K. M.; Camaaño-Moure, A.; Miller, B. L. *Org. Lett.* **2005**, *7*, 733−736.
(14) Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, *6*, 1219−1228.
(15) For a protetive group effect on the course of CM, see: Sheddan, N. A.; Arion, V. B.; Mulzer, J. *Tetrahedron Lett.* **2006**, *47*, 6689−6693.
(16) For representative examples, see: (a) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. J. *Org. Lett.* **2001**, *3*, 2209−2212. (b) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 809−812.
(17) Kadlčíkova, A.; Hrdina, R.; Valterová, I.; Kotora, M. *Adv. Synth. Catal.* **2009**, *351*, 1279−1283.
(18) Crystallographic data (excluding structure factors) for the structures **3aa** and **3ac** have been deposited with the Cambridge Crystallographic Data Centre with CCDC numbers 1038566 and 1038567. Copies of the data can be obtained, free of charge, on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
(19) For selected examples of hydrogenation of α-alkylidene β-lactames using H2, Pd/C, see: (a) Danh, T. T.; Borsuk, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2006**, *62*, 10928−10936. (b) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Adv. Synth. Catal.* **2005**, *347*, 833−838. (c) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Piccinelli, F.; Tolomelli, A. *Org. Lett.* **2005**, *7*, 533−536. (d) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A. *Bioorg. Med. Chem.* **2002**, *10*, 1813−1818. For H_2/Pt/C, see: (e) Tiwari, D. K.; Shaikh, A. Y.; Pavase, L. S.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Tetrahedron* **2007**, *63*, 2524−2534. (f) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575−580. For H_2/PtO_2, see: (g) Buynak, J. D.; Rao, M. N.; Pajouhesh, H.; Chandrasekaran, R. Y.; Finn, K. *J. Org. Chem.* **1985**, *50*, 4245−4252. For $H_2/RhCl(PPh_3)_3$, see: (h) Pentassuglia, G.; Tarzia, G.; Andreotti, D.; Bismara, C.; Carlesso, R.; Donati, D.; Gaviraghi, G.; Perboni, A.; Pezzoli, A.; Rossi, T.; Tamburini, B.; Ursini, A. *J. Antibiot.* **1995**, *48*, 399−407.
(20) For an example of important β-lactam derivatives with *cis* relative stereochemistry, see: (a) Robert, M.; Adlington, R. M.; Baldwin, J. E.; Becker, G. W.; Chen, B.; Cheng, L.; Cooper, S. L.; Hermann, R. B.; Howe, T. J.; McCoull, W.; McNulty, A. M.; Neubauer, B. L.; Pritchard, G. J. *J. Med. Chem.* **2001**, *44*, 1491−1508.
(21) (a) Riant, O. Copper(I) hydride reagents and catalysts. In *Patai's Chemistry of Functional Groups*. John Wiley & Sons: Hoboken, NJ, 2011. (b) Deutsch, C.; Krause, N. *Chem. Rev.* **2008**, *108*, 2916−2927. (c) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293.
(22) Kværnø, L.; Ritter, T.; Werder, M.; Hauser, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4653−4656.
(23) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y.; Liu, L.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9276−9282.
(24) West, P. R.; Davis, G. C. U.S. Patent 4709107, November 24, 1987.
(25) Dooley, B. M.; Bowles, S. E.; Storr, T.; Frank, N. L. *Org. Lett.* **2007**, *9*, 4781−4783.
(26) Hiebel, M.-A.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874−7878.
(27) Otto, H. H.; Mayrhofer, R. *Liebigs Ann. Chem.* **1983**, *1983*, 1162−1168.
(28) Mayrhofer, R.; Otto, H.-H. *Synthesis* **1980**, *1980*, 247−248.
(29) Kværnø, L.; Werder, M.; Hauser, H.; Carreira, E. M. *J. Med. Chem.* **2005**, *48*, 6035−6053.

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