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A Formal Total Synthesis of Virantmycin: A Modular Approach towards Tetrahydroquinoline Natural Products

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A synthesis of an advanced intermediate towards the racemic form of the antiviral agent virantmycin has been developed featuring an intramolecular aza-xylylene Diels–Alder reaction. The required arylthiocarbamate has been constructed using an efficient oxidative cyclization strategy. A novel synthetic approach to chlorine-substituted allylic alcohols using an unprecedented palladium-catalyzed cross-coupling reaction of α,β-unsaturated ketones and protected propargylic alcohols is reported.

Introduction

(–)-Virantmycin (**1**) (Figure 1) is an unusual chlorinated member of the large class of tetrahydroquinoline alkaloids. It was isolated from a strain of Streptomyces nitrosporeus by Ōmura et al.[1] and was found to be a potent DNA and RNA virus inhibitor as well as an antifungal agent.[2] Several total syntheses of racemic (±)-virantmycin (**2**),[3] natural (–)-virantmycin[4] and the unnatural (+)-antipode[5] have been completed to date, stressing the importance and the promising pharmacological profile of the substance.

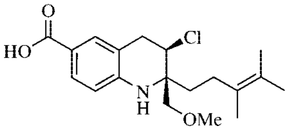

Figure 1. (–)-Virantmycin (**1**).

Various synthetic approaches towards the construction of tetrahydroquinoline ring systems are available, including insertion, ring expansion and ring contraction reactions.[6] However, one of the most versatile and convergent strategies for the construction of tetrahydroquinoline alkaloids is the Diels–Alder reaction of *o*-azaxylylenes which are formed by a 1,4-elimination from a suitable benzylic halide precursor and suitable dienophiles as reported by Nishiyama[7] and Corey.[8] A modified approach developed by our group was applied to the synthesis of several other tetrahydroquinoline natural products.[9]

Results and Discussion

Retrosynthetic Analysis

Our synthetic strategy is based on a published total synthesis of (±)-virantmycin by Corey and Steinhagen whose key steps are summarized in Scheme 1.[3e] The authors used a late stage palladium-catalyzed carboxyesterification/saponification strategy after reductive carbamate opening and establishment of the methyl ether on iodoquinoline **3** which can be obtained from the crucial intramolecular Diels–Alder step. Cyclization precursor **4** is readily available by addition of the simple substrates **5** and **6**, TBS deprotection and subsequent benzylic chlorination. Isocyanate **5** can be synthesized from commercially available 2-aminobenzyl alcohol by iodination with iodine monochloride, TBS protection and isocyanate formation by treatment with phosgene. Allylic alcohol **6** can be obtained in a 6-step reaction sequence starting from methyl vinyl ketone and ethyl propiolate.

With these results in mind, we envisioned a shorter synthesis towards common precursor **3** using our method of carbamate formation[9] which is summarized in Scheme 2. We decided to introduce the iodine atom at a very late stage in our synthetic approach, after cyclization of precursor **8**. This carbamate is formed by a modified reaction type originally developed by Appel.[10] The reaction of an arylthiocarbamate with triphenylphosphane/tetrachloromethane leads to the cleavage of the thiocarbamate upon formation

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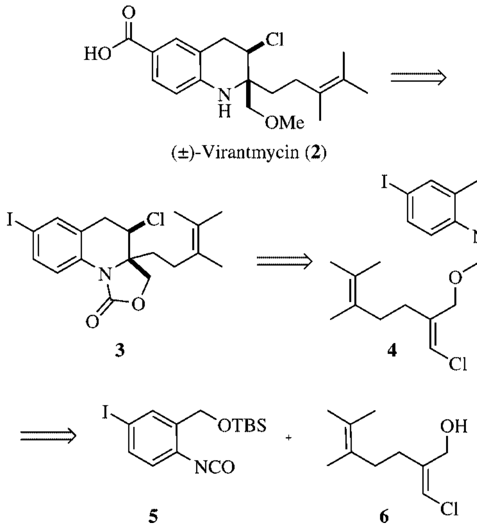
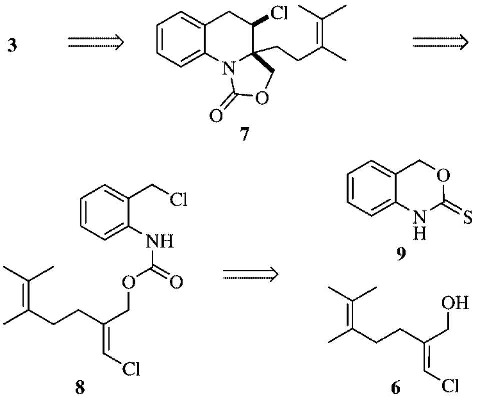


Scheme 1. Corey's retrosynthetic analysis of (±)-virantmycin.

of a benzylic chloride and an isocyanate that can be trapped in situ by a suitable nucleophile, in our case allylic alcohol **6**.

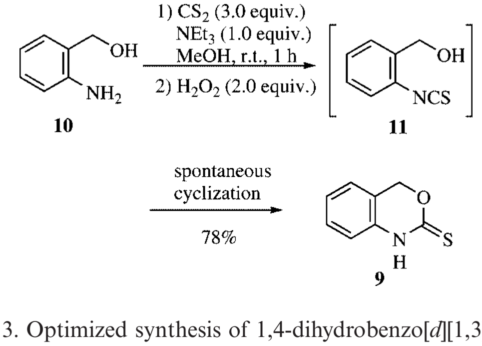


Scheme 2. Modified retrosynthetic analysis towards common precursor **3**.

Optimized Synthesis of 1,4-Dihydrobenzo[*d*][1,3]oxazine-2-thione (9)

One key fragment for our synthetic route towards virantmycin is arylthiocarbamate **9**. This substance has been known for more than 110 years, but synthetic methodologies for its reliable and high-yield formation are scarce. The classical method developed by Paal and Laudenheimer,[11] heating 2-aminobenzyl alcohol (**10**) in carbon disulfide at reflux for several hours without additional solvent leads to formation of the desired product **9** in a maximum yield of 30% which can be raised to about 40%, if the reaction is performed in a sealed vial. A second possibility includes the reaction of 2-azidobenzyl alcohol in the presence of triphenylphosphane in a Staudinger type reaction leading to an iminophosphorane. This intermediate can be reacted with carbon disulfide in a sealed vial at elevated temperature to yield the cyclized product in a yield of 53%.[12] A more effective possibility for the formation of **9** has been proposed by Hirai[13] who used a commercially unavailable thiazolium catalyst along with thiocarbonyl diimidazole which provided the desired product in 74% yield. Thus, while the first two methods clearly suffer from low yields and the consequential problematic purification of the reaction product, the third literature precedent for the synthesis of **9** suffers from the fact that the catalyst is not commercially available and the application of the more expensive thiocarbonyl diimidazole.

We were sure that the low yields of the simplest synthesis, the reaction of 2-aminobenzyl alcohol with carbon disulfide, could be explained by an insufficient tendency for dehydrosulfurization from the occurring intermediate and the reversible character of this reaction step. Thus, our task was to find reagents that are able to remove the sulfur species irreversibly from the reaction. When checking the literature for nonaromatic cyclic thiocarbamates, we found that this could be achieved by the addition of reagents like ethyl chloroformate,[14] lead nitrate,[15] or hydrogen peroxide.[16] Especially the method using hydrogen peroxide seemed appealing to us as it utilises cheap reagents, can be performed without using anhydrous or inert conditions and is very quick. When trying this reaction type on our aromatic substrate **10** we were pleased to find that the cyclized product could be obtained in a yield of 78% in less than 2 hours by stirring 2-aminobenzyl alcohol, carbon disulfide and base in methanol with subsequent addition of hydrogen peroxide which leads to colorization and warming of the reaction mixture and the formation of a sulfur precipitate. Optimization studies revealed that the yield was significantly lower when using less than three equivalents of carbon disulfide which seemed to be the optimal amount. Utilisation of imidazole as base or of other solvents like CH_2Cl_2 does not provide any product; see Scheme 3.

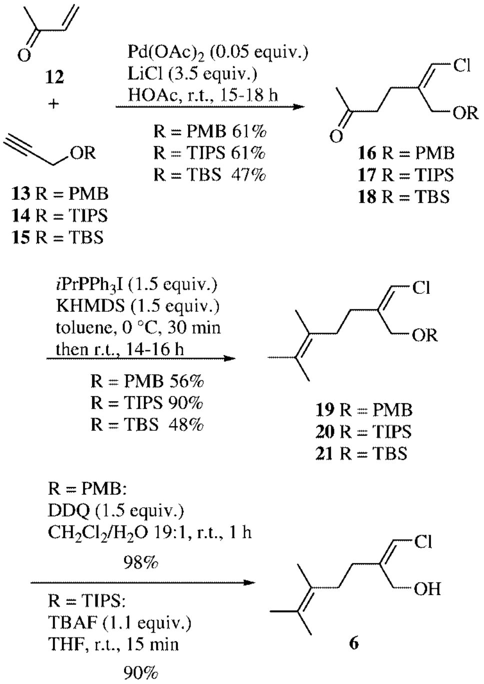


Scheme 3. Optimized synthesis of 1,4-dihydrobenzo[*d*][1,3]oxazine-2-thione (**9**).

In summary, we were able to transfer the oxidative thiocarbamate formation strategy to the synthesis of an aromatic 2-thioxo-1,3-O,N-heterocycle which provides us with a cheap and versatile synthesis of these compounds with a minimum amount of the toxic reagent carbon disulfide. In addition, this synthesis can easily be scaled up to multigram amounts.

A Novel Synthetic Approach Towards 2-Chloromethylene-5,6-dimethylhept-5-en-1-ol (6) and Similar Allylic Alcohols

For the synthesis of allylic alcohol **6**, we relied upon a palladium-catalyzed reaction that is well known for propiolic acid esters.[17] In this reaction type, alkyl propiolates are reacted with α,β-unsaturated aldehydes or ketones, e.g. acrolein or methyl vinyl ketone, under palladium acetate catalysis in the presence of chloride or bromide nucleophiles yielding the desired bromo- or chloro-substituted α,β-unsaturated esters directly. Unfortunately, this creates the necessity to carry out a cumbersome complete reduction – selective protection – oxidation sequence to receive a properly protected derivative. We wanted to develop a reaction sequence that omits these steps and leads directly to the desired protected keto alcohol. This strategy and our results are summarized in Scheme 4.



Scheme 4. Novel synthesis of allylic alcohol **6**.

Thus, we surveyed the direct reaction of a protected propargylic alcohol with methyl vinyl ketone in the presence of palladium acetate. The reaction of propargylic alcohol itself under standard conditions does not lead to the formation of any product but to quick decomposition of the catalyst upon formation of palladium black. To the best of our knowledge, this reaction type has not been investigated up to now, the only resembling example being the reaction of 2-propynyl tosylcarbamate with acrolein in the presence of lithium bromide leading to the bromo-allylic carbamate in a yield of 58%.[18] We chose three propargylic alcohols, a PMB derivate **13** (synthesized by reaction of propargylic bromide with 4-methoxybenzylic alcohol in the presence of sodium hydride in a yield of 92%[19]), a TIPS derivative **14** (reaction of propargylic alcohol with TIPS chloride in the presence of imidazole in a yield of 93%[20]) and a TBS derivative **15** which is commercially available; see Table 1.

Table 1. Optimization of the palladium-catalyzed coupling of **13** with methyl vinyl ketone (**12**).[a]

Entry	Equiv. of $Pd(OAc)_2$	Reaction time [h]	Yield [%]
1	0.02	4	25
2	0.02	6	32
3	0.02	15	34
4	0.03	5	33
5	0.03	15	48
6[b]	0.05	15	61

[a] All reactions were carried out with 4 equiv. of methyl vinyl ketone and 4 equiv. of lithium chloride. [b] Reaction carried out with 3.5 equiv. of lithium chloride.

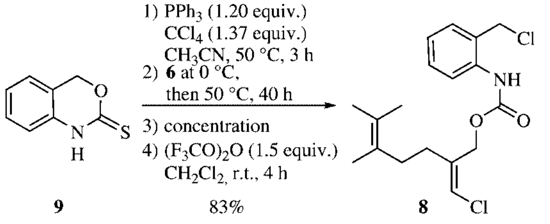
The reaction conditions for the cross-coupling reaction were optimized using the PMB derivative **13**. The results are summarized in Table 1. Entry 1 shows the conditions that were optimal when reacting ethyl propiolate with methyl vinyl ketone, which in the case of **13** resulted in formation of the desired product **16** in 25% yield along with a small amount of the *E*-chloro isomer. The major side reaction was the 1,4-addition of acetic acid (the solvent) to methyl vinyl ketone. This shows that the reaction is relatively slow in comparison to this 1,4-addition. Longer reaction times (entry 2 and 3) did not lead to a significantly increased yield. A higher catalyst loading with short reaction time also did not improve the yield (entry 4). The increase of catalyst loading was still important for good yields, but the reaction of propargylic alcohols proved to be slow. We obtained the best result using 5 mol-% catalyst, 3.5 equiv. lithium chloride and 4 equiv. of methyl vinyl ketone which lead to 61% of the desired product in 15 h (entry 6). When subjecting alcohols **14** and **15** to these optimized reaction conditions we received **17** and **18** uneventfully in 61% and 47% yield, respectively, which has not been optimized. These results show the versatility and robustness of this new reaction type which cuts the former four-step synthesis[3e] to two steps.

Products **16**–**18** were reacted in a Wittig-type reaction[21] using isopropyltriphenylphosphonium iodide. This reaction does not occur when using lithium bases like *n*-butyllithium or lithium bis(trimethylsilyl)amide (LiHMDS) in various solvents, in some cases the reactant even decomposes. When using potassium bis(trimethylsilyl)amide (KHMDS) in toluene solution, the reaction proceeds in all three cases, but with distinct differences in yield. The best yield was obtained for ketone **17** which was transformed to **20** in a yield of 90%. For the PMB derivative **16** and TBS derivative **18**, the desired products **19** and **21** were obtained in yields of 53% and 58%, respectively, along with substantial amounts of unreacted starting material. This ratio could not be altered by using larger excesses of Wittig reagent. We attribute this finding to the fact that the protecting groups PMB and TBS are more acidic than TIPS leading to deprotonation by the Wittig reagent. Additionally, the bulkier TIPS group might prevent deprotonation of the carbonyl group's α-proton which is also quite acidic. The synthesis of unprotected allylic alcohol **6** could be achieved by application of standard deprotection conditions. The PMB group was removed using DDQ in CH_2Cl_2/H_2O[22] in an excellent yield of 98%, while the TIPS group was easily removed using TBAF in THF in a yield of 90%.[23] The deprotection of TBS was not carried out as it did not provide notably better results than PMB while being much more expensive.

In summary, we succeeded in synthesizing key allylic alcohol **6** using a novel palladium-catalyzed cross-coupling reaction. The now three-step synthesis starting from readily available protected propargylic alcohols provides the desired product in a combined yield of 28% (PMB) or 49% (TIPS). The synthesis of derivatives of virantmycin could easily be achieved by using other α,β-unsaturated compounds or nucleophiles, thus providing an entrance into a large class of possible analogues.

Synthesis of Carbamate 8 and Development of an Advanced Purification Strategy

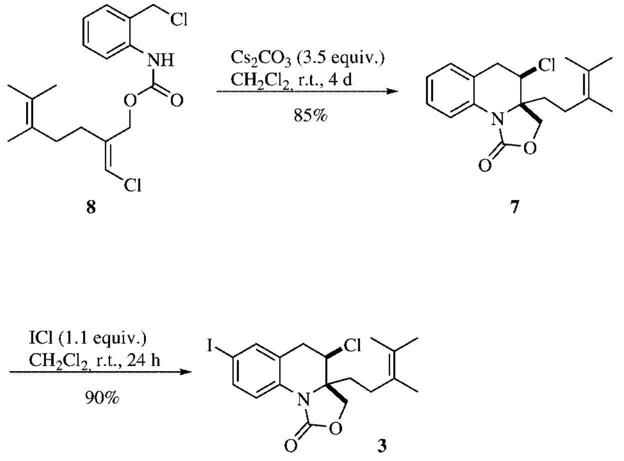
Using allylic alcohol **6**, we started to investigate the reaction of this alcohol in the Appel-type reaction with cyclic thiocarbamate **9**. Using our standard conditions, the reaction proceeded smoothly, but purification of the product proved to be cumbersome as the reaction byproduct triphenylphosphane sulfide cannot be easily removed by column chromatography. Experiments to remove the sulfide by different filtration techniques were unsuccessful, other methods like alkylation with methyl trifluoromethanesulfonate[24] could not be utilized because of possible alkylation of product **8**. So we examined the transformation of triphenylphosphane sulfide to the corresponding oxide by trifluoroacetic anhydride as described by Michalski.[25] As summarized in Scheme 5, we exposed the dissolved crude reaction product in CH_2Cl_2 and treated it with trifluoroacetic anhydride which lead to complete consumption of the sulfide byproduct by formation of the oxide which could be separated much more easily by chromatographic purification. Thus, we were able to synthesize the desired carbamate in 83% isolated yield due to our optimized purification conditions.



Scheme 5. Synthesis of carbamate intermediate **8**.

Completion of the Formal Total Synthesis: Intramolecular Cyclization of Carbamate 8 and Iodination

Having completed the synthesis of advanced carbamate intermediate **8**, the stage was set for the key [4+2] cycloaddition which was performed using the standard conditions from our earlier work in this field.[9] Thus, dry caesium carbonate (several hours at <0.1 Torr and 100 °C) was added to a solution of **8** in dichloromethane and stirring for 4 d at room temperature smoothly provided tricyclus **7** in a yield of 85%. The completion of our synthesis of advanced intermediate **3** could be achieved by aromatic iodination using iodine monochloride in CH_2Cl_2 which provided the desired compound as a single regioisomer in a yield of 90%; see Scheme 6.



Scheme 6. Cyclization and final iodination.

Thus, we have completed the synthesis of the advanced precursor **3** in four consecutive steps starting from **9** in an overall yield of 49%. The remaining steps of the total synthesis towards (±)-virantmycin have already been performed. The corresponding substances have been synthesized, charaterized and published by Corey and Steinhagen. Thus, we have completed a novel modified formal total synthesis of (±)-virantmycin.

Conclusion

In conclusion, we have devised a novel synthesis of the advanced intermediate **3** thus completing a formal total synthesis of (±)-virantmycin as the ongoing steps are already known from literature precedence.[3e] The key intermediate for the [4+2]-Diels–Alder-type cycloaddition, carbamate **8**, can be obtained in 2 steps in a convenient synthesis starting from 2-aminobenzyl alcohol in a combined yield of 61% due to the novel synthetic approach towards aromatic thiocarbamates using oxidative removal of the reaction byproducts and our improved purification protocol using trifluoroacetic anhydride. Following Corey's route, the synthesis of this compound would require five consecutive steps with an overall yield of 55% (calculated from the synthesis of **4** without the first iodination step[3e]). This Appel-type reaction can easily be adapted to other allylic alcohols which makes it suitable for analogue construction. In addition, a novel synthesis of the required allylic alcohol **6** including a new palladium-catalyzed coupling has been developed and optimized shortening the former 6-step sequence (40% overall yield) to four convenient steps (49% for TIPS protection).

Experimental Section

All reactions were carried out in dried glassware in an atmosphere of argon. Solvents were distilled or dried using standard methods prior to use where appropriate. All chemicals were purchased from commercial suppliers and used without further purification. Flash chromatography was performed using silica gel 60 (230–400 mesh provided by Macherey–Nagel). TLC was performed using precoated aluminium foil sheets silica gel 60 F254 provided by Merck. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 400 or DRX 500, using the residual signals of the solvent as standard. Multiplicities are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants J are reported in Hz. Numbers of attached protons in the ^{13}C spectra were elucidated using DEPT90 and 135 and are given in the form: p = primary (RCH_3), s = secondary (R_2CH_2), t = tertiary (R_3CH), q = quaternary (R_4C). Mass spectrometry (MS) as well as high resultion MS (HRMS) was performed on a Finnigan MAT 90 using electron impact (EI) at 70 eV. Ion mass/charge ratios (*m*/*z*) are reported as values in atomic mass units followed by the intensities relative to the base peak in parathenses. Infrared spectra (IR) were obtained on a Bruker IFS 88 as film on KBr and are reported as values in cm^{-1} using the following abbreviations for absorption strength: s = strong, m = medium, w = weak. Elemental analyses were carried out on a Heraeus CHN-O-Rapid and are given as percentage values with the abbreviation calcd. = calculated. Melting points were measured on a MelTemp II apparatus by Labaratory devices. The values are reported in °C and are uncorrected.

1,4-Dihydro-benzo[*d*][1,3]oxazine-2-thione (9):[12] In a two-necked flask with a reflux condenser, 2-aminobenzyl alcohol (3.80 g, 30.3 mmol) was dissolved in MeOH (40 mL) and triethylamine (4.25 mL, 3.06 g, 30.3 mmol) and carbon disulfide (5.48 mL, 6.91 g, 90.8 mmol, 3.0 equiv.) were added with stirring. After 1 h at room temp., hydrogen peroxide (6.30 mL, 60.6 mmol, 2.0 equiv.) was added dropwise in order to keep the solution boiling slightly. The color of the solution changed from orange to black and a yellow precipitate of sulfur was formed. After the addition was completed, the mixture was filtered and the volatiles removed under reduced pressure. The crude product was dissolved in the minimum amount of MeOH and column chromatography (*n*-pentane–Et_2O, 1:1) of this solution provided the product as a beige solid (3.89 g, 23.5 mmol, 78%). Additional purification could be achieved by recrystallization from CH_2Cl_2/hexanes. Compare ref.[12] for spectroscopic data. M.p. 137 °C (CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.36 (s, 2 H, CH_2O), 6.95 (br. d, J = 7.9 Hz, 1 H, Ar-H), 7.11–7.18 (m, 2 H, Ar-H), 7.31 (dd, J = 7.9 Hz, J = 7.6 Hz, 1 H, Ar–H), 10.18 (s, 1 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 69.7 (s), 114.0 (t), 118.1 (q), 124.1 (t), 125.4 (t), 129.8 (t), 133.0 (q), 185.8 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 3190 (m), 3137 (m), 3018 (m), 1624 (m), 1604 (m), 1536 (s), 1498 (m), 1452 (m), 1418 (m), 1321 (m), 1225 (m), 1162 (m), 1108 (m), 971 (m), 892 (m), 859 (m), 758 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): 165 ($[M^+]$, 100), 132 (30), 104 (60), 78 (40). HRMS (C_8H_7NOS): calcd. 165.0248, found 165.0247. C_8H_7NOS (165.21): calcd. C 58.16, H 4.27, N 8.48, found C 57.81, H 4.45, N 8.19.

1-Methoxy-4-[(prop-2-ynyloxy)methyl]benzene (13):[19] To a cooled (0 °C) suspension of sodium hydride (60% in mineral oil, 1.32 g, 33.0 mmol, 1.1 equiv.) in DMF (25 mL), 4-methoxybenzyl alcohol (4.15 g, 30.0 mmol) was added and the mixture was stirred for 25 min. Then propargylic bromide (4.91 g, 33.0 mmol, 1.1 equiv.) was added and the reaction was stirred for 2.5 h at 0 °C and for 1 h at room temp. After cooling to 0 °C, the reaction was quenched by the addition of 0.65 M aqueous potassium carbonate solution (20 mL). After extraction with Et_2O (3 × 50 mL), drying with Na_2SO_4 and concentration in vacuo, the residue was purified by column chromatography (*n*-pentane–Et_2O, 9:1) yielding the product as a yellow oil (4.88 g, 27.7 mmol, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.47 (t, J = 2.4 Hz, 1 H, $C{\equiv}CH$), 3.80 (s, 3 H, OCH_3), 4.14 (d, J = 2.4 Hz, 2 H, OCH_2), 4.54 (s, 2 H, OCH_2 benzylic), 6.88 (br. d, J = 8.3 Hz, 2 H, Ar-H), 7.29 (br. d, J = 8.3 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.3 (p), 56.7 (s), 71.2 (s), 74.6 (t), 79.8 (q), 113.9 (t), 129.3 (q), 129.9 (t), 159.5 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 3288 (m), 3001 (w), 2937 (m), 2907 (m), 2837 (m), 1612 (s), 1585 (m), 1513 (s), 1464 (m), 1442 (m), 1386 (w), 1352 (m), 1302 (m), 1250 (s), 1175 (m), 1079 (s), 1034 (s), 820 (m), 637 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): 176 ($[M^+]$, 53), 136 (48), 121 (100), 78 (12). HRMS ($C_{11}H_{12}O_2$): calcd. 176.0837, found 176.0834. $C_{11}H_{12}O_2$ (176.21): calcd. C 74.98, H 6.86, found C 74.35, H 6.65.

Triisopropyl(prop-2-ynyloxy)silane (14):[20] To a solution of propargylic alcohol (1.52 g, 27.1 mmol) in CH_2Cl_2 (60 mL) was added imidazole (3.69 mg, 54.2 mmol, 2.0 equiv.) followed by triisopropylsilyl chloride (5.75 g, 29.8 mmol, 1.1 equiv.). The mixture was stirred for 18 h, quenched by the addition of H_2O (50 mL) and extracted with Et_2O (3 × 40 mL). The combined extracts were dried with Na_2SO_4, concentrated in vacuo and the remaining residue was purified by column chromatography (*n*-pentane–Et_2O, 9:1) yielding the product as a yellow oil (5.35 g, 25.1 mmol, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03–1.19 (m, 21 H, TIPS), 2.39 (t, 1 H, J = 2.4 Hz, $C{\equiv}CH$), 4.38 (d, 1 H, J = 2.4 Hz, OCH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.0 (t), 17.9 (p), 51.8 (s), 77.6 (t), 82.5 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 3312 (m), 2944 (s), 2892 (m), 2867 (s), 1465 (m), 1384 (w), 1370 (m), 1262 (w), 1102 (s), 1070 (m), 1014 (w), 1000 (m), 920 (w), 882 (m), 773 (m), 683 (m), 660 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): 212 ($[M^+]$, 53), 169 (92), 127 (100), 99 (36), 77 (57), 69 (77). HRMS ($M - C_3H_7$): calcd. 169.1049, found 169.1045. $C_{12}H_{24}OSi$ (212.40): calcd. C 67.86, H 11.39, found C 67.92, H 11.34.

6-Chloro-5-[(4-methoxybenzyloxy)methyl]hex-5-en-2-one (16): To a solution of palladium(II) acetate (162 mg, 0.72 mmol, 0.05 equiv.) in acetic acid (50 mL), lithium chloride (2.15 g, 50.6 mmol, 3.5 equiv.), methyl vinyl ketone (4.06 g, 57.9 mmol, 4.0 equiv.) and 1-methoxy-4-[(prop-2-ynyloxy)methyl]benzene (**13**) (2.55 g, 14.5 mmol) were added at room temp. and turned the solution's color to orange. The mixture was stirred for 18 h and the reaction was then quenched by addition of H_2O (90 mL). The aqueous phase was extracted with Et_2O (150 mL), the organic phase dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 1:1) yielding the desired product as a yellow oil (2.50 g, 8.84 mmol, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.10 (s, 3 H, CH_3), 2.44–2.48 (m, 2 H, CH_2), 2.57–2.61 (m, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 4.18 (d, 2 H, J = 0.9 Hz, CH_2 allylic), 4.41 (s, 2 H, CH_2 benzylic), 6.01 (t, 1 H, J = 0.9 Hz, $C{=}CHCl$), 6.86–6.90 (br. d, 2 H, J = 8.8 Hz, Ar-H), 7.24–7.28 (br. d, 2 H, J = 8.8 Hz, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.3 (s), 30.1 (p), 41.7 (s), 55.4 (p), 66.6 (s), 72.2 (s), 113.9 (t), 116.0 (t), 129.6 (t), 130.2 (q), 138.2 (q), 159.4 (q), 207.6 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 3071 (w), 3000 (w), 2933 (m), 2858 (w), 2838 (w), 1715 (s), 1612 (m), 1586 (w), 1513 (s), 1464 (m), 1441 (m), 1359 (m), 1302 (m), 1248 (s), 1173 (m), 1081 (m), 1034 (m), 923 (w), 820 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): 282 ($[M^+]$, 0.2), 137 (83), 121 (100), 77 (5). HRMS ($C_{15}H_{19}ClO_3$): calcd. 282.1023, found 282.1025. $C_{15}H_{19}ClO_3$ (282.76): calcd. C 63.71, H 6.77, found C 63.78, H 6.95.

6-Chloro-5-[(triisopropylsilanyloxy)methyl]hex-5-en-2-one (17): To a solution of palladium(II) acetate (147 mg, 0.66 mmol, 0.05 equiv.)

in acetic acid (45 mL), lithium chloride (649 mg, 15.3 mmol, 3.5 equiv.), methyl vinyl ketone (1.22 g, 17.5 mmol, 4.0 equiv.) and triisopropyl(prop-2-ynyloxy)silane (**14**) (1.00 g, 4.37 mmol) were added at room temp. and turned the solution's color to orange. The mixture was stirred for 15 h and the reaction was then quenched by addition of H_2O (90 mL). The aqueous phase was extracted with Et_2O (150 mL), the organic phase dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 9:1) yielding the desired product as a yellow oil (856 mg, 2.68 mmol, 61 %). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.03–1.16 (m, 21 H, TIPS), 2.10 (s, 3 H, CH_3), 2.44–2.48 (m, 2 H, CH_2), 2.57–2.65 (m, 2 H, CH_2), 4.18 (s, 2 H, CH_2 allylic), 6.01 (br. s, 1 H, C=CHCl) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.0 (t), 17.9 (p), 26.6 (s), 29.8 (p), 42.2 (s), 60.9 (s), 112.4 (t), 140.8 (q), 207.6 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 2943 (w), 2893 (w), 2867 (m), 1720 (m), 1463 (w), 1134 (w), 1100 (w), 1013 (w), 918 (w), 882 (m), 789 (w), 682 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): no [M^+], 275 (100), 109 (45), 43 (59). HRMS (M – C_3H_7): calcd. 275.1234, found 275.1232. $C_{16}H_{31}ClO_2Si$ (318.95): calcd. C 60.25, H 9.80, found C 60.37, H 9.82.

5-[(*tert*-Butyldimethylsilanyloxy)methyl]-6-chlorohex-5-en-2-one (18): To a solution of palladium(II) acetate (33 mg, 0.15 mmol, 0.05 equiv.) in acetic acid (15 mL), lithium chloride (436 mg, 10.3 mmol, 3.5 equiv.), methyl vinyl ketone (823 mg, 11.7 mmol, 4.0 equiv.) and commercially available *tert*-butyldimethyl(prop-2-ynyloxy)silane (**15**) (500 mg, 2.94 mmol) were added at room temp. and turned the solution's color to orange. The mixture was stirred for 15 h and the reaction was then quenched by addition of H_2O (25 mL). The aqueous phase was extracted with Et_2O (50 mL), the organic phase dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 9:1) yielding the desired product as a yellow oil (380 mg, 1.37 mmol, 47 %). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.07 (s, 6 H, 2× $SiCH_3$), 0.89 (br. s, 9 H, 3× CH_2), 2.13 (s, 3 H, CH_3), 2.40–2.48 (m, 2 H, CH_2), 2.51–2.65 (m, 2 H, CH_2), 4.15 (s, 2 H, CH_2 allylic), 5.90 (br. s, 1 H, C=CHCl) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = –5.0 (p), 18.4 (q), 26.6 (p), 26.7 (s), 29.8 (p), 42.0 (s), 66.4 (s), 123.2 (t), 133.8 (q), 207.7 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 2955 (m), 2930 (m), 2894 (w), 2857 (m), 1719 (m), 1471 (w), 1361 (w), 1254 (m), 1129 (m), 1098 (w), 1072 (m), 837 (m), 777 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): 276 ([M^+], 0.1), 221 (55), 219 (100), 109 (83), 93 (38), 43 (93). $C_{13}H_{25}ClO_2Si$ (276.87): calcd. C 56.39, H 9.10, found C 56.61, H 9.24.

1-{[2-(Chloromethylene)-5,6-dimethylhept-5-enyloxy]methyl}-4-methoxybenzene (19): A suspension of isopropyltriphenylphosphonium iodide (6.98 g, 16.6 mmol, 1.5 equiv.) in toluene (50 mL) was cooled to 0 °C and potassium bis(trimethylsilyl)amide (0.5 M in toluene, 32.3 mL, 16.6 mmol, 1.5 equiv.) was added. The orange suspension was stirred for 30 min, then **16** (3.05 g, 10.7 mmol) was added and the now turbid solution was stirred for 16 h at room temp. The reaction was quenched by the addition of H_2O (400 mL) and extracted with Et_2O (4 × 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 7:3) yielding unreacted **16** (515 mg, 1.82 mmol) along with the desired product as yellow oil (1.83 g, 6.13 mmol, 56 %, 69 % based on recovered starting material). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.62 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 2.14–2.18 (m, 2 H, CH_2), 2.21–2.25 (m, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 4.22 (d, 2 H, *J* = 0.9 Hz, CH_2 allylic), 4.43 (s, 2 H, CH_2 benzylic), 5.96 (t, 1 H, *J* = 0.9 Hz, C=CHCl), 6.86–6.90 (br. d, 2 H, *J* = 8.8 Hz, Ar-H), 7.26–7.30 (br. d, 1 H, *J* = 8.8 Hz, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.5 (p), 20.2 (p), 20.7 (p), 31.5 (s), 33.2 (s), 55.4 (p), 66.6 (s), 72.1 (s), 113.9 (t), 114.8 (t), 125.1 (q), 126.8 (q), 129.6 (t), 130.4 (q), 139.9 (q), 159.4 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 2995 (w), 2918 (m), 2858 (w), 1612 (w), 1586 (w), 1514 (m), 1463 (w), 1357 (w), 1302 (w), 1249 (m), 1173 (w), 1084 (m), 1037 (m), 820 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%): 308 ([M^+], 0.5), 203 (5), 136 (4), 121 (100), 83 (11), 55 (7). HRMS ($C_{18}H_{25}ClO_2$): calcd. 308.1543, found 308.1540. $C_{18}H_{25}ClO_2$ (308.84): calcd. C 70.00, H 8.16, found C 70.12, H 7.92.

{[2-(Chloromethylene)-5,6-dimethylhept-5-enyl]oxy}triisopropylsilane (20): A suspension of isopropyltriphenylphosphonium iodide (2.74 g, 6.34 mmol, 1.5 equiv.) in toluene (70 mL) was cooled to 0 °C and potassium bis(trimethylsilyl)amide (0.5 M in toluene, 12.7 mL, 6.34 mmol, 1.5 equiv.) was added. The orange suspension was stirred for 30 min, then **17** (1.35 g, 4.23 mmol) was added and the now turbid solution was stirred for 14 h at room temp. The reaction was quenched by the addition of H_2O (50 mL) and extracted with Et_2O (3 × 70 mL). The combined extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 9:1) yielding the desired product as a yellow oil along with inseparable impurities (1.97 g, 5.71 mmol, 90 %). The product was used as such in the subsequent reaction. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.03–1.16 (m, 21 H, TIPS), 1.60 (s, 9 H, 3× CH_3), 2.07–2.17 (m, 2 H, CH_2), 2.22–2.29 (m, 2 H, CH_2), 4.37 (d, 2 H, *J* = 1.2 Hz, CH_2 allylic), 5.71 (br. s, 1 H, C=CHCl) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.3 (p), 18.0 (p), 18.3 (p), 20.1 (p), 20.5 (p), 30.9 (s), 33.2 (s), 60.5 (s), 112.4 (t), 124.9 (q), 126.9 (q), 142.5 (q) ppm.

***tert*-Butyl-{[2-(chloromethylene)-5,6-dimethylhept-5-enyl]oxy}-dimethylsilane (21):** A suspension of isopropyltriphenylphosphonium iodide (770 mg, 1.78 mmol, 1.5 equiv.) in toluene (10 mL) was cooled to 0 °C and potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.56 mL, 1.78 mmol, 1.5 equiv.) was added. The orange suspension was stirred for 30 min, then **18** (310 mg, 1.18 mmol) was added and the now turbid solution was stirred for 15 h at room temp. The reaction was quenched by the addition of H_2O (15 mL) and extracted with Et_2O (3 × 25 mL). The combined extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 9:1) yielding the desired product as yellow oil (174 mg, 0.57 mmol, 48 %). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.09 (s, 6 H, 2× $SiCH_3$), 0.91 (br. s, 9 H, 3× CH_3), 1.63 (s, 9 H, 3× CH_3), 2.07–2.15 (m, 2 H, CH_2), 2.24–2.30 (m, 2 H, CH_2), 4.37 (d, 2 H, *J* = 1.2 Hz, CH_2 allylic), 5.81 (br. s, 1 H, C=CHCl) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = –5.4 (p), 18.1 (q), 18.4 (p), 20.1 (p), 20.6 (p), 25.9 (p), 30.8 (s), 33.2 (s), 66.5 (s), 111.8 (t), 126.7 (q), 132.6 (q), 142 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 2955 (m), 2929 (m), 2857 (m), 1471 (w), 1374 (w), 1255 (w), 1120 (w), 1076 (w), 838 (m), 777 (m). MS (EI, 70 eV): *m*/*z* (%): 302 ([M^+], 0.9), 245 (25), 189 (18), 135 (69), 83 (100), 55 (26) cm^{-1}. HRMS ($C_{16}H_{31}ClOSi$): calcd. 302.1833, found 302.1839. $C_{16}H_{31}ClOSi$ (302.96): calcd. C 63.43, H 10.31, found C 63.24, H 10.12.

2-(Chloromethylene)-5,6-dimethylhept-5-en-1-ol (6). From PMB-Protected Precursor 19: To a solution of **19** (100 mg, 0.32 mmol) in CH_2Cl_2/pH 7 buffer, 19:1 (4 mL) was added DDQ (111 mg, 0.49 mmol, 1.5 equiv.) at room temp. The green solution was stirred for 60 min whereupon a yellow precipitate was formed. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The phases were separated and the organic phase was dried with Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (*n*-pentane–Et_2O, 6:1) yielding the desired product as a pale yellow oil (60 mg, 0.32 mmol, 98 %).

From TIPS-Protected Precursor 20: To a solution of **20** (1.46 g, 4.23 mmol) in THF (40 mL) was added tetrabutylammonium fluoride trihydrate (1.22 g, 4.65 mmol, 1.1 equiv.) in THF (10 mL) at room temp. and the mixture was stirred for 15 min. The reaction was then quenched with H_2O (20 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 6:1) yielding the product as a pale yellow oil (719 mg, 3.81 mmol, 90 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.63 (s, 9 H, 3× CH_3), 1.86 (br. s, 1 H, OH), 2.14–2.18 (m, 2 H, CH_2), 2.21–2.25 (m, 2 H, CH_2), 4.31 (s, 2 H, CH_2OH), 5.88 (s, 1 H, C=CHCl) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.4 (p), 20.2 (p), 20.7 (p), 31.6 (s), 33.2 (s), 60.4 (s), 114.2 (t), 125.4 (q), 126.6 (q), 141.9 (q). IR (film on KBr): $\tilde{\nu}$ = 3337 (m), 3068 (w), 2987 (m), 2921 (m), 1632 (w), 1600 (w), 1446 (m), 1373 (w), 1315 (w), 1263 (w), 1234 (w), 1159 (w), 1019 (m), 864 (w), 807 (m). MS (EI, 70 eV): *m/z* (%): 188 ([M$^+$], 3), 153 (12), 83 (100), 55 (39), 41 (35). HRMS ($C_{10}H_{17}ClO$): calcd. 188.0968, found 188.0965. $C_{10}H_{17}ClO$ (188.69): calcd. C 63.65, H 9.08, found C 63.82, H 9.31.

2-(Chloromethylene)-5,6-dimethylhept-5-enyl [2-(Chloromethyl)-phenyl]carbamate (8): To a solution of **9** (345 mg, 2.09 mmol) and triphenylphosphane (657 mg, 2.50 mmol, 1.20 equiv.) in acetonitrile (20 mL) was added tetrachloromethane (440 mg, 2.86 mmol, 1.37 equiv.) and the mixture was stirred at 50 °C for 3 h, changing the color from pale yellow to orange. It was then cooled to 0 °C, **6** (660 mg, 3.50 mmol, 1.67 equiv.) was added and the mixture was stirred at 50 °C for 40 h. After cooling, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), trifluoroacetic anhydride (658 mg, 3.14 mmol, 1.5 equiv.) was added, stirred for 4 h at room temp. The reaction was again concentrated to dryness. The residue was subjected to column chromatography (*n*-pentane–Et_2O, 1:1) providing the product as a beige solid (624 mg, 1.80 mmol, 83 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.57 (9 H, 3× s, 3× CH_3), 2.11–2.14 (m, 2 H, CH_2), 2.15–2.18 (m, 2 H, CH_2), 4.55 (s, 2 H, CH_2Cl), 4.88 (d, 2 H, *J* = 0.9 Hz, OCH_2 allylic), 5.96 (t, 1 H, *J* = 0.9 Hz, C=CHCl), 6.91 (br. s, 1 H, NH), 7.05 (ddd, 1 H, *J* = 7.5 Hz, *J* = 7.5 Hz, *J* = 1.0 Hz, Ar-H), 7.22 (dd, 1 H, *J* = 7.5 Hz, *J* = 1.4 Hz, Ar-H), 7.32 (ddd, 1 H, *J* = 7.5 Hz, *J* = 7.5 Hz, *J* = 1.4 Hz, Ar-H), 7.79 (d, 1 H, *J* = 7.5 Hz, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.3 (p), 20.1 (p), 20.6 (p), 31.3 (s), 33.1 (s), 43.9 (s), 62.4 (s), 116.3 (t), 122.9 (t), 124.6 (t), 125.5 (q), 126.2 (q), 127.3 (q), 130.1 (t), 130.2 (t), 136.6 (q), 137.4 (q), 153.5 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 3288 (s), 3124 (m), 3072 (m), 2981 (m), 2924 (s), 2867 (m), 2726 (w), 2318 (w), 2063 (w), 1947 (w), 1918 (w), 1887 (w), 1696 (s), 1593 (s), 1545 (s), 1457 (s), 1372 (m), 1252 (s), 1071 (s), 908 (w), 806 (m), 677 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 355 ([M$^+$], 1.5), 170 (6), 135 (5), 83 (10), 58 (58), 43 (100). HRMS ($C_{18}H_{23}Cl_2NO_2$): calcd. 355.1108, found 355.1106. $C_{18}H_{23}Cl_2NO_2$ (356.29): calcd. C 60.68, H 6.50, N 3.93, found C 60.76, H 6.65, N 4.20.

4-Chloro-3a-(3,4-dimethylpent-3-enyl)-3,3a,4,5-tetrahydrooxazolo-[3,4-*a*]quinolin-1-one (7): To a solution of **10** (300 mg, 0.84 mmol) in CH_2Cl_2 was added dried caesium carbonate (960 mg, 2.95 mmol, 3.5 equiv.) and the mixture was stirred at room temp. for 4 d. The reaction mixture was then filtered through a plug of celite with subsequent washing with CH_2Cl_2. The filtrate was concentrated in vacuo. The crude product was purified by column chromatography (*n*-pentane–Et_2O, 1:1) yielding the product as a white solid (228 mg, 0.71 mmol, 85 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.55–1.70 (m, 2 H, CH_2), 1.93–2.06 (m, 2 H, CH_2), 3.18 (dd, 1 H, *J* = 18.4 Hz, *J* = 1.6 Hz, CHClCH_AH_B), 3.42 (dd, 1 H, *J* = 18.4 Hz, *J* = 4.7 Hz, CHClCH_AH_B), 4.26 (d, 1 H, *J* = 8.8 Hz, OCH_AH_B), 4.35 (dd, 1 H, *J* = 4.7 Hz, *J* = 1.6 Hz, CHCl), 4.52 (d, 1 H, *J* = 8.8 Hz, OCH_AH_B), 6.98–7.14 (m, 2 H, Ar-H), 7.22–7.28 (m, 1 H, Ar-H), 7.98 (br. d, 1 H, *J* = 8.4 Hz, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.3 (p), 19.9 (p), 20.6 (p), 27.8 (s), 33.5 (s), 33.6 (s), 57.8 (t), 63.3 (s), 68.9 (q), 120.7 (t), 120.8 (q), 124.4 (t), 124.8 (q), 125.9 (q), 127.8 (t), 129.4 (t), 132.9 (q), 154.9 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 3491 (w), 3068 (m), 2924 (m), 2863 (m), 2727 (w), 1753 (s), 1605 (w), 1582 (m), 1493 (m) 1458 (m), 1400 (m), 1369 (m), 1351 (m), 1309 (m), 1268 (m), 1220 (m), 1188 (m), 1157 (m), 1108 (m), 1057 (m), 1027 (m), 986 (m), 960 (m), 821 (s), 708 (m), 685 (m), 661 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%): 319 ([M$^+$], 45), 284 (10), 222 (100), 186 (18), 142 (37), 55 (9). HRMS ($C_{18}H_{22}ClNO_2$): calcd. 319.1339, found 319.1334. $C_{18}H_{22}ClNO_2$ (319.83): calcd. C 67.60, H 6.93, N 4.38, found C 67.55, H 7.12, N 4.18.

4-Chloro-3a-(3,4-dimethylpent-3-enyl)-7-iodo-3,3a,4,5-tetrahydro-oxazolo[3,4-*a*]quinolin-1-one (3): To a solution of **7** (150 mg, 0.47 mmol) in CH_2Cl_2 (6 mL), iodine monochloride (84 mg, 0.52 mmol, 1.1 equiv.) and the mixture was stirred for 24 h at room temp. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ solution (10 mL). After speration of the phases, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-pentane–Et_2O, 1:1) yielding the product as a brown solid (188 mg, 0.42 mmol, 90 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.51 (s, 3 H, CH_3), 1.74 (s, 6 H, 2× CH_3), 1.98–1.87 (m, 2 H, CH_2), 2.10–1.99 (m, 2 H, CH_2), 3.21 (dd, 1 H, *J* = 18.6 Hz, *J* = 1.5 Hz, CHClCH_AH_B), 3.51 (dd, 1 H, *J* = 18.6 Hz, *J* = 4.7 Hz, CHClCH_AH_B), 4.28 (d, 1 H, *J* = 9.0 Hz, OCH_AH_B), 4.42 (dd, 1 H, *J* = 4.7 Hz, *J* = 1.5 Hz, CHCl), 4.60 (d, 1 H, *J* = 9.0 Hz, OCH_AH_B), 7.52 (br. s, 1 H, Ar-H), 7.62 (dd, 1 H, *J* = 8.7 Hz, *J* = 1.9 Hz, Ar-H), 7.84 (br. d, 1 H, *J* = 8.7 Hz, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.0 (p), 28.6 (p), 28.9 (p), 31.0 (s), 31.6 (s), 33.0 (s), 56.7 (t), 63.0 (s), 68.8 (q), 75.5 (q), 78.3 (q), 88.2 (q), 122.5 (t), 123.0 (q), 132.6 (q), 136.9 (t), 138.2 (t), 154.4 (q) ppm. IR (film on KBr): $\tilde{\nu}$ = 2964 (m), 2926 (m), 1855 (w), 1758 (m), 1487 (m), 1398 (m), 1361 (w), 1322 (w), 1295 (w), 1261 (m), 1221 (w), 1098 (m), 1026 (m), 966 (w), 872 (w), 802 (m), 750 (w) ppm. MS (EI, 70 eV): *m/z* (%): no [M$^+$], 319 (15), 222 (10), 97 (13), 84 (86), 49 (100). $C_{18}H_{21}ClINO_2$ (445.72): calcd. C 48.50, H 4.75, N 3.14, found C 48.76, H 4.61, N 3.32.

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[1] S. Ōmura, A. Nakagawa, H. Hashimoto, R. Oiwa, Y. Iwai, A. Hirano, N. Shibukawa, Y. Kojima, *J. Antibiot.* **1980**, *33*, 1395–1396.

[2] A. Nakagawa, Y. Iwai, H. Hashimoto, N. Miyazaki, R. Oiwa, Y. Takahashi, A. Hirano, N. Shibukawa, Y. Kojima, S. Ōmura, *J. Antibiot.* **1981**, *34*, 1408–1415.

[3] a) M. L. Hill, R. A. Raphael, *Tetrahedron Lett.* **1986**, *27*, 1293–1296; b) M. L. Hill, R. A. Raphael, *Tetrahedron Lett.* **1990**, *46*, 4587–4594; c) Y. Morimoto, F. Matsuda, H. Shirahama, *Synlett* **1991**, 201–203; d) Y. Morimoto, F. Matsuda, H. Shirahama, *Tetrahedron* **1996**, *52*, 10609–10630; e) H. Steinhagen, E. J. Corey, *Org. Lett.* **1999**, *1*, 823–824.

[4] a) M. Ori, N. Toda, K. Takami, K. Tago, H. Kogen, *Angew. Chem.* **2003**, *115*, 2644–2647; *Angew. Chem. Int. Ed.* **2003**, *42*, 2540–2543; b) T. G. Back, J. E. Wulff, *Angew. Chem.* **2004**, *116*, 6655–6658; *Angew. Chem. Int. Ed.* **2004**, *43*, 6493–6496; c) M.

Ori, N. Toda, K. Takami, K. Tago, H. Kogen, *Tetrahedron* **2005**, *61*, 2075–2104.

[5] Y. Morimoto, H. Shirahama, *Tetrahedron* **1996**, *52*, 10631–10652.

[6] A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *48*, 15031–15070.

[7] K. Nishiyama, H. Kubo, T. Sato, K. Higashiyama, S. Ohmiya, *Heterocycles* **1998**, *46*, 1103–1106.

[8] H. Steinhagen, E. J. Corey, *Angew. Chem.* **1999**, *111*, 2054–2056; *Angew. Chem. Int. Ed.* **1999**, *38*, 1928–1931.

[9] F. Avemaria, S. Vanderheiden, S. Bräse, *Tetrahedron* **2003**, *59*, 6785–6796.

[10] R. Appel, *Angew. Chem.* **1975**, *87*, 863–874; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811.

[11] C. Paal, E. Laudenheimer, *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2978–2980.

[12] P. Molina, A. Arques, A. Molina, *Synthesis* **1991**, 21–23.

[13] H. Sugimoto, I. Makino, K. Hirai, *J. Org. Chem.* **1988**, *53*, 2263–2267.

[14] a) F. Fulop, G. Csinrinyi, G. Bernat, J. Szabo, *Synthesis* **1985**, 1148–1149; b) A. Kjaer, R. Gmelin, R. B. Jensen, *Acta Chem. Scand.* **1956**, *10*, 432–438.

[15] a) M. G. Ettlinger, *J. Am. Chem. Soc.* **1950**, *72*, 4792–4796; b) M. Menard, A. M. Wrigley, F. L. Chubb, *Can. J. Chem.* **1961**, *39*, 273–277.

[16] G. Li, T. Ohtani, *Heterocycles* **1997**, *45*, 2471–2474.

[17] Z. Wang, X. Lu, *J. Org. Chem.* **1996**, *61*, 2254–2255.

[18] A. Lei, X. Lu, *Org. Lett.* **2000**, *2*, 2699–2702.

[19] G. Guanti, S. Perozzi, R. Riva, *Tetrahedron: Asymmetry* **2002**, *13*, 2703–2726.

[20] E. Piers, T. Wong, K. A. Ellis, *Can. J. Chem.* **1992**, *70*, 2058–2064.

[21] G. Wittig, G. Geissler, *Justus Liebigs Ann. Chem.* **1953**, *580*, 44–57.

[22] T. Yoshioka, Y. Oikawa, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885–888.

[23] M. Ueki, *Yuki Gosei Kagaku Kyokaishi* **1990**, *48*, 1042–1043.

[24] J. Omelańczuk, M. Mikolajczyk, *J. Am. Chem. Soc.* **1979**, *101*, 7292–7295.

[25] J. Hélinski, Z. Skrzypczyński, J. Wasiak, J. Michalski, *Tetrahedron Lett.* **1990**, *31*, 4081–4084.

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