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Stereoselective synthesis of tetrazole CB92834, a potent retinoid compound

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Abstract—An improved, convergent synthesis of CB92834 is relying on a Suzuki cross-coupling reaction and easily allows multigram-scale preparation of the compound. The approach features three highly stereoselective steps.

1. Introduction

The increasing incidence of cancer in the world has induced massive efforts aiming at the development of the most efficient treatments of the disease.[1] Among the various approaches, chemoprevention is the use of non-cytotoxic therapeutic intervention at the early stages of carcinogenesis against the development and progression of mutant clones to invasive cancer. The chemopreventive potential of retinoids has been the focus of much attention over the last decade.[2] Retinoids are defined as molecules related to all-*trans*-retinoic acid, and for which biological activities are mediated by two types of receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs).[3] With respect to the various isotypes of these receptors, the retinoids-induced effects include modifications of (i) cell proliferation, (ii) apoptosis (cell death) and (iii) reversal of premalignancy by inducing differentiation processes. Retinoids have been shown to be active on breast, lung, cervical and head and neck cancers, as well as on neuroblastoma and acute promyelocytic leukemia. Although much important data has been obtained, the exact signaling pathways required for retinoids to exert their biological effects remain elusive.[4]

Recently, a class of 1,2-bisaryl alkenes featuring a *Z* configuration has been reported as displaying promising activities on RARs and RXRs.[5] The foremost representative of this class of compound is tetrazole **9**.[6] However, the published preparation of **9** suffers from several drawbacks which impede its use on multigram-scale synthesis. Not only is it linear, but it also relies on a Wittig reaction between the phosphorus ylid generated from phosphonium salt **5** (prepared from toluene (**2**) in three steps) and *p*-cyanoacetophenone (**6**) to create the carbon–carbon double bond featuring the requisite *Z* configuration (Scheme 1). The reaction is reported as being poorly stereoselective, delivering a 7:3 mixture of *Z* and *E* isomers (**7** and **8**, respectively). In addition, it suffers from a tedious separation procedure of the two isomers, requiring three sequential chromatography on silica to isolate the desired one **7** in only 35% yield. Attemps to either improve the stereoselectivity of this step or isomerize the *E* isomer into the *Z*, all failed in our hands.[7] We describe below a much improved preparation of **9** which allows easy, multi-gram scale synthesis of the compound.

The design of a more efficient synthesis of the target compound required the stereocontrolled production of the vinyl C–C double bond with the requisite *Z* stereochemistry. We chose to exploit the well-documented stereoselectivity of a Suzuki cross-coupling reaction between boronate **10** (subunit A) and *Z* vinyl bromide **11** (subunit B) (Scheme 2).[8]

Preparation of subunit A was accomplished through the three step sequence depicted in Scheme 3. Thus, bromide **12** was produced by a double Friedel–Crafts alkylation of bromobenzene and the resultant aryl bromide was transformed into boronate **10** by the method of Miyaura.[9,10] The use of $Pd(dppf)Cl_2$ proved to be particularly efficient, allowing a low loading of catalyst (1 mol%) and the isolation of **10** in good yield by simple distillation.

Quite obvious was the fact that the success of the new approach heavily depended on our ability to

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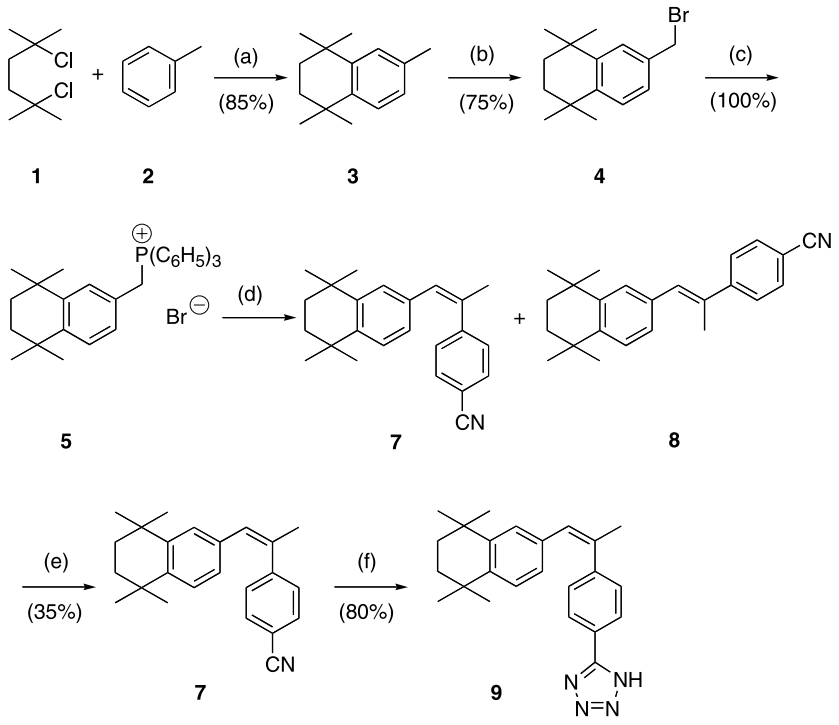
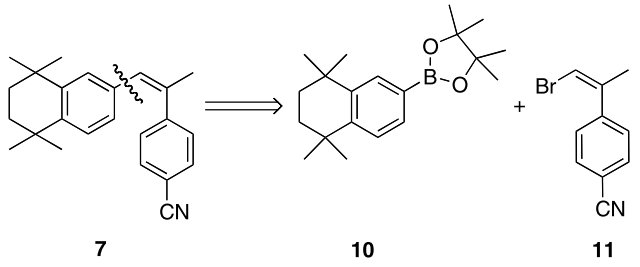


Scheme 1. Published synthesis of tetrazole **9**. Reagents and conditions: (a) $AlCl_3$, 110 °C; (b) *N*-bromosuccinimide, CH_2Cl_2; (c) $P(C_6H_5)_3$; (d) *n*-BuLi, 4-cyanoacetophenone (**6**); (e) three sequential chromatography separations; (f) Me_3SiN_3, $(n\text{-}Bu_3Sn)_2O$.

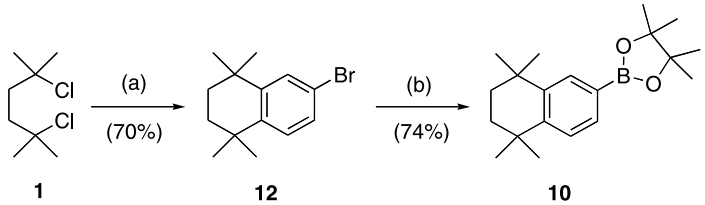


Scheme 2. Stereoselective approach to **7**

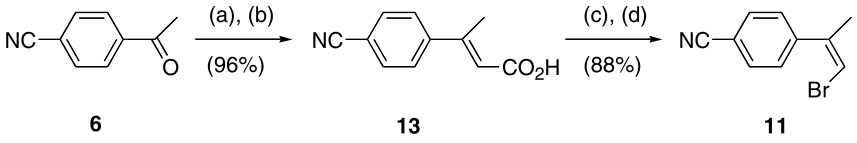
stereoselectively generate vinyl bromide **11**, with the requisite *Z* stereochemistry. Acid **13** was stereoselectively produced by a Wadsworth–Emmons reaction between ketone **6** and triethyl phosphonoacetate in dry ethanol followed by saponification and protonation of the resultant product (Scheme 4). The *Z/E* isomer ratio was found to strongly depend on the solvent. Thus, carrying out the Wadsworth–Emmons reaction in diethyl ether or tetrahydrofuran (THF) led to a 3:7 mixture in favor of the *E* isomer. Conducting the reaction in ethanol, however, led to an increase of the selectivity to 98:2. Hydrolysis of the ester group led to the desired acid, and a simple crystallisation from methanol allowed the isolation of the pure *E* isomer **13** in virtually quantitative yield.[11] A sequence of bromination/decarboxylative debromination proved to be particularly gratifying, delivering exclusively the *Z* vinyl bromide **11** in 88% yield, the result of an *anti* elimination of bromide.[12,13] The whole sequence of reactions (four steps) required a single purification by distillation and compound **11** could easily be produced on multi-gram scale without experiencing a drop in yields.

Coupling of subunits A and B (boronate **10** and vinyl bromide **11**) could again be achieved on multi-gram scale and was found to be completely stereoselective: product **7** was the sole isomer detected in the crude sample (Scheme 5).[14] Purification of this material reproducibly afforded the desired compound **7** in 71–74% isolated yield. Production of the tetrazole cycle present in the final product was then carried out on multi-gram scale according to literature procedure.[15] Treating (**7**) at 110 °C for 12 h with trimethylsilyl azide in the presence of a catalytic amount of bis-(tri-*n*-butyltin)oxide furnished target molecule **9** in 80% isolated yield.

Thus, this new, convergent approach allows the preparation of **9** with a global yield of 30%; three of the five steps of the

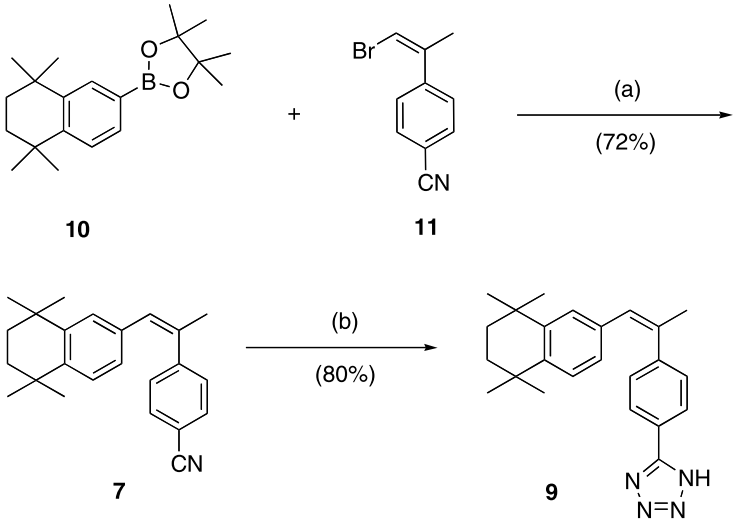


Scheme 3. Synthesis of subunit A. Reagents and conditions: (a) $AlCl_3$, bromobenzene; (b) bis-(pinacolato)diboron, KOAc, $Pd(dppf)Cl_2$ (1 mol%).



6 13 11

Scheme 4. Stereocontrolled synthesis of subunit B. Reagents and conditions: (a) dry ethanol, sodium, triethylphosphonoacetate; (b) KOH, methanol; (c) Br_2, $CHCl_3$; (d) dry acetone, K_2CO_3.



10 11 7 9

Scheme 5. Coupling of subunits A and B. Reagents and conditions: (a) $NaHCO_3$, $Pd(dppf)Cl_2$; (b) $TMSN_3$, $[n\text{-}Bu)_3Sn]_2O$ (10 mol%).

sequence (i. e., **6**→**13**, **13**→**11**, **10**+**11**→**7**) are highly stereoselective, providing the desired isomer in excess of 98% in each case. The synthesis is applicable to large-scale production of **9** and is potentially useful for the preparation of analogues structurally related to the parent compound.

2. Experimental

2.1. General

Unless otherwise stated, ^1H NMR, ^{13}C NMR spectra were recorded in deuterated chloroform on a Brucker AM200 spectrometer operating at 200 and 50 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) relative to $(CH_3)_4Si$ (^1H) and $CDCl_3$, (^{13}C). IR spectra were recorded on a FT-IR spectrometer. Combustion data were obtained from the analytical department of the University of Rouen. Commercially available chemicals were used without further purification.

2.1.1. (*E*) 3-(4-Cyanophenyl)-but-2-enoic acid (13). Sodium (3.5 g) is added in small portion to dry ethanol (250 mL). When reaction of the metal is complete, the solution is cooled down to 0 °C and neat triethylphosphonoacetate (30 g, 137 mmol) is added. After 15 min of stirring at the same temperature, the solution is warmed up to room temperature and a solution of 4-cyanoacetophenone (**6**) (20 g, 138 mmol) in dry ethanol (25 mL) is added dropwise. The resultant red solution is stirred for 30 min, after which period of time the solvent is evaporated. Extraction with 10% aqueous $NaHCO_3$/AcOEt, drying over $MgSO_4$ and evaporation yield 30 g of the desired ethyl ester as a 98:2 mixture of *E*/*Z* isomers. This crude material is then hydrolyzed by stirring overnight at room temperature in a solution of potassium hydroxide (16 g) in methanol (200 mL). Addition of concentrated HCl at 0 °C until pH=4 results in the precipitation of a white solid. Filtration, sequential washing of the solid with water and methanol, and drying in vacuum yield 25 g of pure (*E*) acid **13** (96% over two steps). Mp (methanol)=192 °C. ^1H NMR (DMSO-d_6) δ 7.64 (d, J=8.2 Hz, 2H), 7.53 (d, J=8.2 Hz, 2H), 6.02 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 167.8, 152.2, 145.9, 132.5, 127.2, 119.7, 118.8, 111.3, 17.1. IR (neat) ν 3448, 2258, 1654, 1026 cm^{-1}. Calcd for $C_{10}H_8BrN$: C, 71.03; H, 4.26. Found: C, 71.72; H, 5.02.

2.1.2. (*Z*) 1-Bromo-2-(4-cyanophenyl)propene (11). To a suspension of acid **13** (25 g, 134 mmol) in chloroform (300 mL) at 0 °C is added bromine (23.5 g, 146 mmol) and the resultant mixture is stirred for 12 h. The reaction can be monitored by ^1H NMR spectrometry (δ 7.7 (m, 4H), 5.0 (s, 1H), 2.52 (s, 3H)). The clear orange solution is then evaporated and the residue is dissolved in dry acetone (250 mL); $NaHCO_3$ (15 g) is added and the mixture is refluxed for 16 h. Filtration and evaporation under reduced pressure deliver a crude, oily residue which is partitioned between water and ethyl acetate. The water layer is extracted with additional AcOEt and the combined organic layers are dried over magnesium sulfate. Evaporation under reduced pressure and distillation (154 °C/0.5 mbar) give 16.5 g of product **11** as a colorless liquid (88% yield). ^1H NMR ($CDCl_3$) δ 7.60 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 6.27 (s, 2H), 2.1 (s, 3H). ^{13}C NMR ($CDCl_3$) δ

144.8, 140.0, 132.0, 128.6, 118.6, 111.2, 103.5, 24.4. IR (neat) ν 3072, 2914, 2850, 2228, 1604, 1500, 842 cm^{-1}. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.12; H, 3.67; N, 6.57.

2.1.3. 1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-bromonaphthalene (12). To dry CH_2Cl_2 (20 mL) at 0 °C are sequentially added aluminium trichloride (5.6 g, 42 mmol), neat 2,5-dicloro-2,5-dimethylhexane[16] (20 g, 109 mmol) and a solution of bromobenzene (17.2 g, 109.3 mmol) in CH_2Cl_2 (20 mL). The mixture is warmed up to room temperature and stirred overnight. It is then slowly poured onto crushed ice (100 g). Extraction with AcOEt (200 mL), decantation, washing of the organic layer with 10% aqueous $NaHCO_3$ (100 mL), drying of the organic layer over magnesium sulfate and evaporation of the volatiles left an oily residue which was subjected to distillation (150 °C/0.5 mbar) to furnish 18.9 g of **12** (70% yield). ^1H NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.22 (d, $J=8.8$ Hz, 2H), 7.16 (d, $J=8.8$ Hz, 2H), 1.65 (s, 4H), 1.25 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 147.4, 143.8, 141.7, 129.6, 129.0, 128.6, 35.1, 34.2, 32.0. IR (neat) ν 2960, 1458, 1364, 908, 816, 734 cm^{-1}. Calcd for $C_{14}H_{19}Br$: C, 63.20; H, 7.10. Found: C, 63.42; H, 6.81.

2.1.4. 1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-pinacolatoboronaphthalene (10). Compound **12** (6.3 g, 23.6 mmol), bis-(pinacolato)diboron (5.0 g, 19.7 mmol), Pd(dppf)Cl_2 (140 mg, 0.19 mmol (1 mol%)) and potassium acetate (5.2 g, 59.1 mmol) are sequentially added to degassed dimethyl sulfoxide (DMSO) (40 mL) under inert atmosphere. The reaction is carried out at 80 °C for 20 h. After cooling, the mixture is poured into water and extracted with AcOEt. The organic layer is evaporated and the residue is dissolved in a 1:1 mixture of heptane/AcOEt (15 mL) and filtered over a plug of silica gel. Washing with additional heptane/AcOEt (1:1) (10 mL) and evaporation of the volatiles delivers the crude product (10 g). Distillation (130 °C/0.5 mbar) yields 5.5 g (74%) of pure product **10**. ^1H NMR ($CDCl_3$) δ 7.75 (s, 1H), 7.55 (d, $J=8.0$ Hz, 1H), 7.28 (d, $J=8.0$ Hz, 2H), 1.66 (s, 4H), 1.3 (s, 12H), 1.26 (s, 12H). IR (neat) ν 2962, 2953, 1362, 1146, 1116, 852, 756 cm^{-1}. Calcd for $C_{20}H_{31}BO_2$: C, 76.43; H, 9.98. Found: C, 76.90; H, 10.49.

2.1.5. (*Z*) 4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propenyl]benzonitrile (7). Bromide **11** (3.7 g, 16.9 mmol), boronate **10** (5.3 g, 16.9 mmol), Pd(dppf)Cl_2 (124 mg, 0.17 mmol (1 mol%)) and $NaHCO_3$ (4.3 g, 50.3 mmol) are sequentially placed in a flask containing a degassed mixture of 1,4-dioxane (60 mL) and water (25 mL) under nitrogen. The reaction is stirred at 80 °C for 20 h. After cooling, the mixture is poured into water and extracted with AcOEt. Evaporation of the volatiles, filtration of the residue through silica and elution with heptane/AcOEt (2:1) give 4.0 g (72%) of product **7**. Mp=121–123 °C (lit.[5]: 95–97 °C).[17] ^1H NMR ($CDCl_3$) δ 7.58 (d, $J=8.4$ Hz, 2H), 7.32 (d, $J=8.4$ Hz, 2H), 7.12 (d, $J=8.0$ Hz, 1H), 6.79 (s, 1H), 6.75 (d, $J=87.0$ Hz, 1H), 6.54 (s, 1H), 2.20 (s, 3H), 1.61 (s, 4H), 1.23 (s, 6H), 1.00 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 148.3, 144.7, 144.0, 135.9, 134.0, 132.8, 129.7, 129.2, 127.9, 126.8, 126.7, 119.4, 110.8, 35.4, 35.4, 34.5, 34.3, 32.2, 32.0, 26.9. IR (neat) ν 2975, 2962, 2228, 1216, 756 cm^{-1}. Calcd for $C_{24}H_{27}N$: C, 87.49; H, 8.26; N, 4.25. Found: C, 87.51; H, 8.38; N, 4.23.

2.1.6. 5-{4-[1-Methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-phenyl}-1*H*-tetrazole 9. Nitrile **7** (3 g, 9.12 mmol), trimethylsilyl azide (3.15 g, 27.4 mmol) and bis-(tri-*n*-butyltin)oxide (540 mg, 0.91 mmol (10 mol%)) are added to toluene (10 mL). The reaction flask is flushed with nitrogen and the mixture is heated at 110 °C for 12 h. The mixture is then cooled down, the volatiles are removed under reduced pressure and the residue is filtered through silica which is washed with a 98:2 mixture of heptane/AcOEt. The solvents are evaporated and the resultant white solid is recrystallized from heptane to deliver 2.7 g (80%) of **9**. Mp=192–193 °C (lit.[5]: 191–193 °C). ^1H NMR ($CDCl_3$) δ 8.04 (d, $J=8.4$ Hz, 2H), 7.38 (d, $J=8.4$ Hz, 2H), 7.03 (d, $J=8.0$ Hz, 2H), 6.83 (s, 1H), 6.72 (d, $J=8.0$ Hz, 2H), 6.48 (s, 1H), 2.19 (s, 3H), 1.53 (s, 4H), 1.16 (s, 6H), 0.92 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 156.6, 147.2, 144.7, 143.7, 136.4, 134.2, 130.0, 128.6, 128.3, 127.9, 126.6, 126.5, 121.9, 35.4, 34.4, 34.2, 32.1, 31.9, 27.2. IR (neat) (ν 3420, 2962, 2856, 1614, 1490, 1456, 1362, 908, 732 cm^{-1}. Calcd for $C_{24}H_{28}N_4$: C, 77.32%; H, 7.53%. Fd: C, 77.61%; H, 7.63%.

Acknowledgements

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respectively. Attempts to isomerize the *E* double bond to its *Z* isomer (e.g., irradiation (mercury lamp) of solutions of pure **7** or **8** in dichloromethane in the presence of $(PhSe)_2$ (10 mol%)) were unsuccessful, invariably producing 1:1 mixtures of the two isomers.

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