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Synthesis of a Selective Estrogen Receptor Degrader via a Stereospecific Elimination Approach

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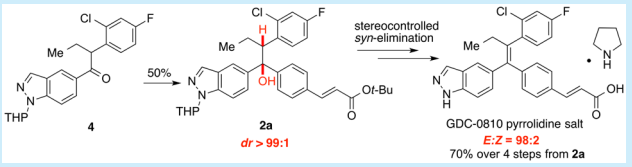
Supporting Information

ABSTRACT: An efficient synthesis of a selective estrogen receptor degrader, GDC-0810, bearing a challenging stereodefined (*E*)-tetrasubstituted all-carbon olefin core, is reported. The described synthetic route involves a highly diastereoselective addition of an arylmagnesium reagent **3a** to ketone **4**, yielding the key tertiary alcohol **2a** in >99:1 dr. The corresponding *tert*-butyl carbonate derivative was identified among other leaving groups to provide the desired olefin geometry in a 98:2 *E*/*Z* ratio via a concerted elimination. A four-step telescoped process was then developed starting from the tertiary alcohol **2a** to produce GDC-0810 API as a pyrrolidine salt in 70% yield.



Selective estrogen receptor modulators and degraders (SERM/SERD) represent an important class of compounds for the treatment of estrogen receptor positive (ER+) breast cancer.[1] Inspired by the first-in-class tamoxifen,[2] an approved therapeutic agent for the treatment and prevention of breast cancer,[3] there have been extensive discovery chemistry efforts focusing on the development of the next generation SERM/SERD therapy.[4] A common structural feature of these compounds is a tetrasubstituted all-carbon olefin core that often poses a synthetic challenge with respect to control of regio- and stereochemistry.[5] GDC-0810 is a SERD currently in clinical development for the treatment of ER+ breast cancer (Figure 1).

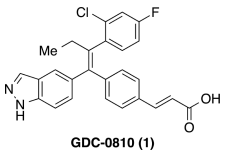
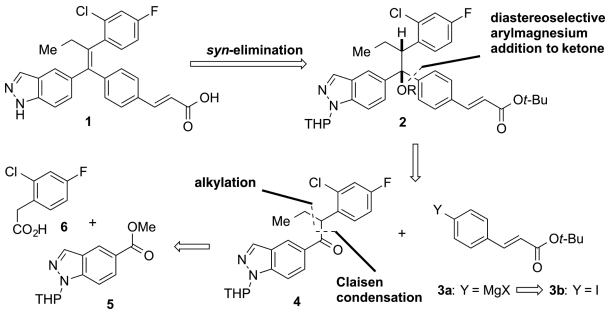


Figure 1. Structure of SERD GDC-0810 (**1**).

The medicinal chemistry synthesis of GDC-0810 suffered from several liabilities precluding its use on large scale.[6] In this paper, we demonstrate efficient access to the challenging tetrasubstituted olefin core through a highly stereocontrolled *syn*-elimination approach.[7]

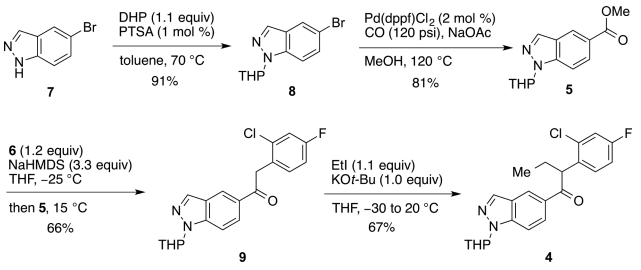
Our retrosynthetic analysis is shown in Scheme 1. We envisioned that the tetrasubstituted olefin found in GDC-0810 (**1**) could be accessed via a concerted elimination of tertiary alcohol derivative **2**. The corresponding tertiary alcohol would be generated via a diastereoselective addition of arylmagnesium species **3a** to ketone **4** consistent with the Felkin−Anh model.[8] 5-Indazolyl ketone **4** would be prepared from Claisen condensation of the 5-indazolyl methyl ester **5** and phenylacetic acid **6**.

Scheme 1. Retrosynthetic Analysis



The synthesis of the 5-indazolyl ketone **4** is depicted in Scheme 2. Commercially available 5-bromoindazole **7** was protected with 3,4-dihydro-2*H*-pyran to selectively form the

Scheme 2. Synthesis of 5-Indazolyl Ketone 4



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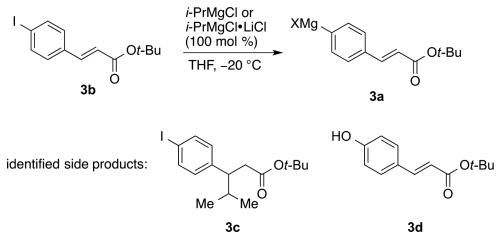
corresponding 1-THP-indazole **8** followed by Pd-catalyzed carbonylation to give methyl ester **5** in 74% yield over two steps. Following a literature procedure,[9] formation of the sodium dianion of phenylacetic acid **6** using NaHMDS at −25 °C followed by addition of methyl ester **5** in THF afforded ketone **9** in 66% isolated yield. Subsequent α-alkylation of ketone **9** with iodoethane and potassium *tert*-butoxide in THF yielded key intermediate **4** in 67% yield.

With ketone **4** in hand, we began to investigate the synthesis of the tertiary alcohol **2a** via reaction with functionalized arylmagnesium reagent **3a**.[10] *trans*-Iodocinnamate **3b** underwent halogen−magnesium exchange with either *i*-PrMgCl or *i*-PrMgCl·LiCl at −20 °C to give arylmagnesium **3a** (Scheme 3).

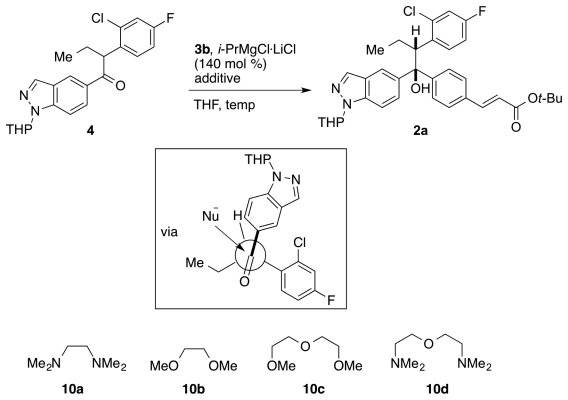
Scheme 3. Synthesis of Arylmagnesium Reagent 3a



Careful examination of the impurity profile of this reaction revealed two major impurities with the proposed structures shown in Scheme 3 on the basis of HRMS analysis. Impurity **3c** (ca. 10 A % HPLC) stemmed from a 1,4-addition of *i*-PrMgCl to cinnamate **3b**. Phenol **3d** (5−10 A % HPLC) was presumed to be a side product from oxidation of arylmagnesium reagent **3a**.[11]

Given the formation of these impurities, *trans*-iodocinnamate **3b** and *i*-PrMgCl·LiCl were used in slight excess (140 mol % of each) relative to ketone **4** to form the arylmagnesium reagent **3a** for the addition reaction. Under these conditions at 0 °C, only 74% conversion of ketone **4** could be achieved with a 66% assay yield of desired product **2a** as determined by quantitative HPLC analysis (Table 1, entry 1). Increasing the reaction temperature to 20 °C improved the conversion to 87%, but the yield of **2a** diminished to 57% (Table 1, entry 2). The incomplete conversions under these conditions suggested a potential stability issue with the arylmagnesium reagent **3a**, which was further evaluated at different temperatures. At 0 °C, **3a** was found to display poor stability with approximately 20% decomposition within a few hours based on quantitative HPLC analysis. A solvent screen was conducted to evaluate if any improvement to stability and, hence, yield could be gained, however THF proved to be the superior solvent. Further reducing the reaction temperature to −20 °C also offered no advantage to the stability of **3a** and displayed unacceptably slow rate of reaction. Next, we evaluated a number of additives including $CeCl_3$,[12] TMEDA (**10a**), DME (**10b**), diglyme (**10c**),[13] and bis(2-dimethylaminoethyl) ether (**10d**)[14] in an effort to improve the stability of **3a**. Additives such as $CeCl_3$ and TMEDA led to incomplete halogen−metal exchange and formation of multiple new impurities (Table 1, entries 3 and 4). The runs using additives **10b** and **10c** did not show much improvement compared to the ones without additives at either 0 or 20 °C (Table 1, entries 5−7). However, bis(2-dimethylaminoethyl)ether (**10d**) was found to improve the stability of the resulting arylmagnesium reagent **3a** presumably by moderating the reactivity through the formation of a chelating magnesium complex.[14] As a result, we were able to achieve 96% conversion at 20 °C with a 76% assay

Table 1. Optimization of Arylmagnesium Addition to Ketone 4



entry	additive (mol %)	temp (°C)	conv[a] (%)	**2a**[b] (%)
1	none	0	74	66
2	none	20	87	57
3	$CeCl_3$ (140)	0	65	54
4	**10a** (140)	0	33	33
5	**10b** (140)	0	73	70
6	**10b** (140)	20	76	59
7	**10c** (140)	0	69	57
8	**10d** (140)	0	84	72
9	**10d** (140)	20	96	76

[a]Determined on the basis of consumption of ketone **4** by quantitative HPLC analysis against a reference standard. [b]Quantitative assay yield based on HPLC analysis of the organic layer after aqueous workup.

yield of **2a** (Table 1, entries 8 and 9). The reaction proceeded with high stereoselectivity producing the product **2a** with >99:1 diastereomeric ratio that was confirmed by HPLC analysis.[15] Based on X-ray crystallographic analysis of **2a**, we found the relative configuration of the tertiary alcohol product to be consistent with predictions based on the Felkin−Anh model for carbonyl additions (Figure 2).[8]

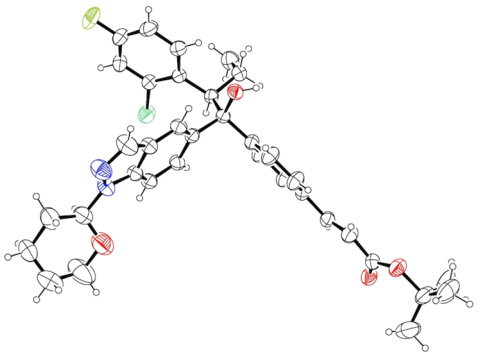


Figure 2. Molecular structure of tertiary alcohol **2a** with 50% probability ellipsoids.

We next investigated the derivatization and stereocontrolled elimination of tertiary alcohol **2a** with the objective to develop a scalable process affording a high *E*/*Z* ratio of the tetrasubstituted olefin **11**, and ultimately GDC-0810, from a concerted *syn*-elimination manifold. A number of derivatives of tertiary alcohol **2a** including imidates,[16] esters,[7b] carbonates,[17] carbamates,[18] and phosphates were readily prepared using NaHMDS or KHMDS[9] and evaluated for the key elimination step. Among those, esters, carbonates, and carbamates were found to be promising and

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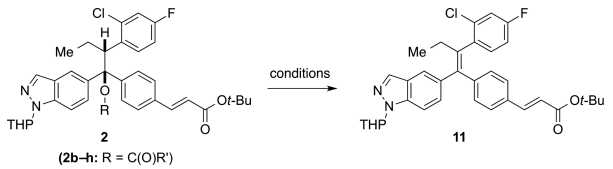
selected for further examination. In contrast to our recent report of highly stereoselective *syn*-elimination via a phosphate derivative,[19] diphenyl phosphate **2i** (see Scheme 1, compound **2**, where R = P(O)(OPh)$_2$) was found to be unstable, spontaneously eliminating even at −30 °C to generate the olefin in poor stereoselectivity (*E*/*Z* = 2:1). In addition, preparation of the trichloroacetimidate[20] of **2a** suffered from poor conversion and low product yield, and thus attempts to synthesize this compound were abandoned.

In agreement with the moderate *E*/*Z* ratio reported in the literature[9] for the concerted *syn*-elimination of the ester derivative of a tertiary alcohol, we observed a 90:10 *E*/*Z* ratio when pivalate **2b** was subjected to the elimination conditions at 150 °C using HMDS as the base and xylene as the solvent (Table 2, entry 1). In the case of an acyl leaving group, addition of base

Table 2. Elimination of Tertiary Alcohol Derivatives[a]



entry	cmpd	R'	base	solvent	temp (°C) /time (h)	**11** (%)[b]	*E*/*Z*
1	**2b**	*t*-Bu	HMDS	xylene	150/24	98	90:10
2	**2b**	*t*-Bu	-	anisole	150/24	87	86:14
3	**2b**	*t*-Bu	K_2CO_3	anisole	150/24	94	97:3
4	**2b**	*t*-Bu	K_2CO_3	anisole	130/40	56	98:2
5	**2c**	Me	K_2CO_3	anisole	150/24	95	97:3
6	**2d**	NMe_2	-	anisole	150/24	95	95:5
7	**2e**	OMe	K_2CO_3	anisole	110/4	98	91:9
8	**2e**	OMe	-	anisole	110/4	96	92:8
9	**2f**	O*i*-Bu	-	toluene	110/23	92	94:6
10	**2g**	O*i*-Pr	-	anisole	130/3	100	93:7
11	**2h**	O*t*-Bu	-	anisole	130/7	96	96:4
12	**2h**	O*t*-Bu	-	PhEt	130/24	90	97:3
13	**2h**	O*t*-Bu	-	PhEt	110/48	91	98:2

[a]Reaction conditions: **2b–h** (0.150 mmol, 100 mol %), base (300 mol %), solvent (30 mL/g). [b]Based on HPLC analysis.

was required to neutralize the carboxylic acid byproduct and prevent isomerization of the desired olefin product (Table 2, entry 2). We further optimized the reaction conditions in a high-throughput experimentation approach.[21] From this screen, the optimal conditions were identified as potassium carbonate and anisole providing a significantly higher *E*/*Z* ratio of 97:3 (Table 2, entry 3). Under these conditions, complete consumption of the starting material pivalate was achieved at 150 °C after 24 h, but only 56% conversion was observed after 40 h at 130 °C (Table 2, entry 4). Similarly, the high temperature of 150 °C was needed to eliminate other ester derivatives such as acetate **2c** (Table 2, entry 5). Although we had obtained good selectivity, the required high temperature was at the edge of our desired operating range for the reaction to maintain reproducible performance during scale-up. Our optimization work then focused on developing elimination conditions that could be conducted at 130 °C or lower, while maintaining reasonable rate of elimination, and obtain the tetrasubstituted olefin **11** in a > 96:4 *E*/*Z* ratio and a high yield. We next evaluated the other two lead families of leaving groups: carbamates and carbonates. In contrast to the ester case, the nonacidic byproducts from elimination of carbonates and carbamates did not have any negative impact on the *E*/*Z* ratio of the resulting tetrasubstituted olefin (Table 2, entries 7 and 8), and therefore, base was not needed in these cases. The carbamates also required high temperature to maintain reasonable rate of elimination exemplified by the case of dimethyl carbamate **2d** (Table 2, entry 6). Gratifyingly, carbonate derivatives showed promise with respect to the minimum reaction temperature. The methyl carbonate **2e** underwent elimination at 110 °C, albeit with only a 92:8 *E*/*Z* ratio (Table 2, entry 8). Examination of other leaving groups including *i*-Bu (**2f**), *i*-Pr (**2g**), and *t*-Bu (**2h**) in the carbonate family revealed a correlation between the increased steric hindrance of the leaving groups and the higher elimination temperature required, although fortunately all were optimized to achieve good conversion at no higher than 130 °C (Table 2, entries 8–11). The highest selectivity of the desired *E*-isomer (96:4) was achieved with the *tert*-butyl carbonate **2h**, and this could further be increased to 97:3 by switching the solvent from anisole to ethylbenzene (Table 2, entry 12). By lowering the reaction temperature further to 110 °C, we were able to obtain the desired tetrasubstituted olefin **11** in 91 A % HPLC and a 98:2 *E*/*Z* ratio from **2h** at the expense of a longer reaction time of 48 h (Table 2, entry 13).

In order to gain a preliminary understanding of the elimination mechanism, we compared the rate of elimination of *tert*-butyl carbonate **2h** with the corresponding deuterium-labeled **2h** in a competition experiment and observed a secondary kinetic isotope effect (KIE, k_H/k_D = 1.3).[15] Although the observed KIE does not support a concerted *syn*-elimination pathway, it is consistent with an asynchronous concerted[22] E1 elimination pathway that we proposed for the synthesis of all-carbon tetrasubstituted olefins via elimination of phosphates supported by DFT calculations.[19] Basically, the dissociation step to form a stabilized carbocation is followed by a very fast deprotonation step with stereochemistry scrambling minimized.

With the optimal *tert*-butyl carbonate leaving group identified, we further developed a four-step telescoped process from tertiary alcohol **2a** to the pyrrolidine salt of GDC-0810 (Scheme 4). The derivatization of **2a** was conducted in ethylbenzene using (Boc)$_2$O and NaHMDS. Upon reaction completion, the resulting mixture containing product **2h** was heated to 130 °C in the same pot to initiate the elimination without any workup. The elimination was found to perform consistently using crude vs purified **2h**, providing the desired tetrasubstituted olefin **11** in an *E*/*Z* ratio of 97:3. Subsequent global deprotection using H_2SO_4 in conjunction with formic acid as a cation scavenger, followed by pyrrolidine salt formation and final crystallization yielded GDC-0810 pyrrolidine salt in 70% overall yield with a 98:2 *E*/*Z* ratio. The absolute stereochemistry of GDC-0810 was unambiguously assigned by single-crystal X-ray diffraction (Figure 3).

In conclusion, we have identified an efficient route to GDC-0810 API that features a highly diastereoselective Grignard reaction of ketone **4** to provide the tertiary alcohol **2a** followed by a *syn*-elimination of *tert*-butyl carbonate derivative **2h** to afford the (*E*)-tetrasubstituted olefin core with excellent stereocontrol. We also developed and demonstrated a telescoped process at

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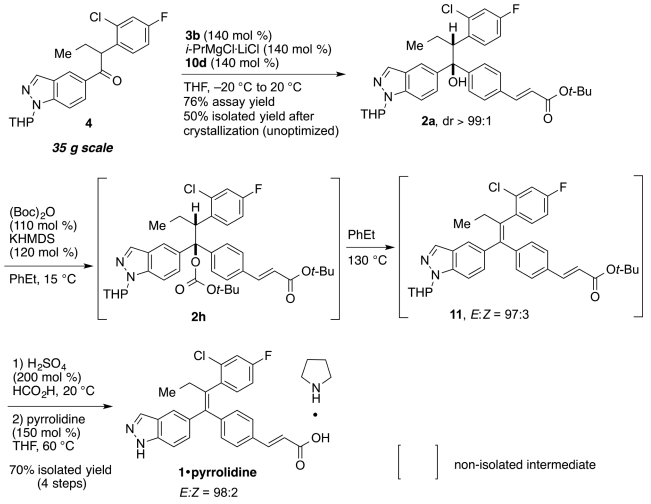
Scheme 4. Synthesis of 1·Pyrrolidine via a Telescoped Sequence



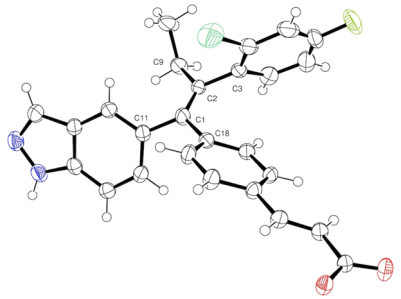


Figure 3. Molecular structure of GDC-0810 (**1**) pyrrolidine salt with 50% probability ellipsoids. Pyrrolidine is omitted for clarity.

decagram scale from tertiary alcohol **2a** to GDC-0810 pyrrolidine salt in 70% yield over four steps with a 98:2 *E*/*Z* ratio.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00035.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1812777−1812778 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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