JOC The Journal of Organic Chemistry

Article

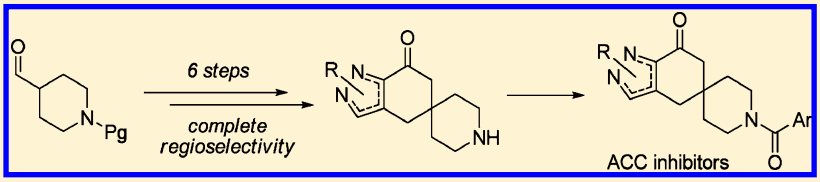
pubs.acs.org/joc

# Synthesis of 7-Oxo-dihydrospiro[indazole-5,4′-piperidine] Acetyl-CoA Carboxylase Inhibitors

Scott W. Bagley,* James A. Southers, Shawn Cabral, Colin R. Rose, David J. Bernhardson, David J. Edmonds, Jana Polivkova, Xiaojing Yang, Daniel W. Kung, David A. Griffith, and Scott J. Bader

Pfizer Worldwide Research & Development, Eastern Point Road, Groton, Connecticut 06340, United States

Supporting Information




**ABSTRACT:** Synthesis of oxo-dihydrospiroindazole-based acetyl-CoA carboxylase (ACC) inhibitors is reported. The dihydrospiroindazoles were assembled in a regioselective manner in six steps from substituted hydrazines and protected 4-formylpiperidine. Enhanced regioselectivity in the condensation between a keto enamine and substituted hydrazines was observed when using toluene as the solvent, leading to selective formation of 1-substituted spiroindazoles. The 2-substituted spiroindazoles were formed selectively from alkyl hydrazones by ring closure with Vilsmeier reagent. The key step in the elaboration to the final products is the conversion of an intermediate olefin to the desired ketone through elimination of HBr from an *O*-methyl bromohydrin. This methodology enabled the synthesis of each desired regioisomer on 50−75 g scale with minimal purification. Acylation of the resultant spirocyclic amines provided potent ACC inhibitors.

## INTRODUCTION

Metabolic perturbations leading to hepatic and intramyocellular lipid accumulation have been hypothesized to contribute to the molecular pathogenesis of insulin resistance and type 2 diabetes mellitus (T2DM).[1] Acetyl-CoA carboxylase (ACC), a central regulator of lipid metabolism, catalyzes the conversion of acetyl-CoA to malonyl-CoA. Malonyl-CoA is an essential and rate limiting substrate for the *de novo* synthesis of fatty acids.[2] Furthermore, malonyl-CoA acts to control fatty acid oxidation through allosteric inhibition of carnitine palmitoyltransferase 1, which is responsible for movement of long chain fatty acyl-CoAs into the mitochondria for $\beta$-oxidation. Consequently, inhibition of ACC is expected to simultaneously block *de novo* lipogenesis and promote fatty acid oxidation. As a result, inhibition of ACC may offer a promising avenue for T2DM treatment by reducing ectopic lipid accumulation and consequently improving insulin sensitization.[3] Pfizer has been pursuing ACC inhibitors (Figure 1) starting with a series of bis-piperidine compounds, exemplified by CP-640186 (**1**),[3] and spirochromanones such as **2**.[4,5] Most recently, the pyrazole spiropyranone (**3**) has been identified as a potent inhibitor of ACC.[6] The chromanone-like spirocyclic core of **3** is synthesized through an efficient sequence of condensation reactions (via **4** and **5**, Scheme 1).[7] However, pyrazoles with alkyl substitution on the isomeric nitrogen were not readily accessed through this sequence and the SAR of that region of the molecule was left unexplored. In addition, compound **3** is prone to a base-mediated retro-Michael type ring-opening reaction and subsequent olefin migration resulting in the presumed open-chain isomer **6**. As part of our continued investigation into

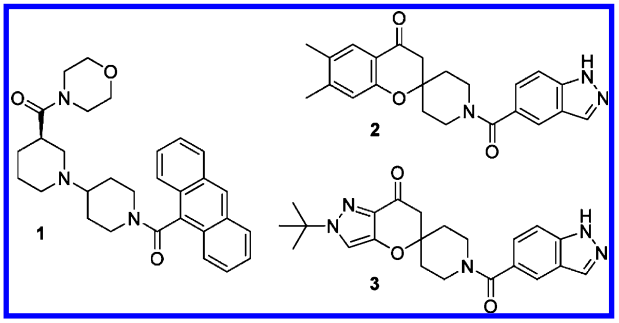



**Figure 1.** Examples of Pfizer ACC inhibitors.

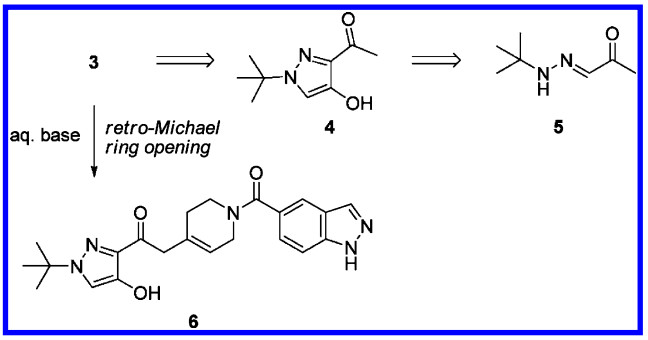
ACC inhibitors, we were interested in preparing oxo-dihydrospiroindazoles in which the ether linkage in **3** would be replaced by a methylene, obviating the retro-Michael ring-opening. We also wished to incorporate regioselective synthetic routes to explore substitution at $N_1$ and $N_2$ of the pyrazole (indazole numbering), resulting in compounds of type **A** and **B** (Figure 2).

**Retrosynthetic Analysis to $N_1$ Alkyl Compounds.** We considered several possible routes to form the oxo-dihydrospiroindazole core and reasoned that a late-stage formation of the central ketone ring, as used previously in the synthesis of **3**, would not be feasible.[4] In addition, the SAR of **3** indicated that bulky *N*-substituents would be preferred; therefore, routes relying on alkylation were initially discounted in favor of

**Received:** November 17, 2011
**Published:** January 12, 2012

 © 2012 American Chemical Society  dx.doi.org/10.1021/jo202377g | *J. Org. Chem.* 2012, 77, 1497−1506

**Scheme 1. Retro-Michael Fate of 3 and Presumed Olefin Isomer**



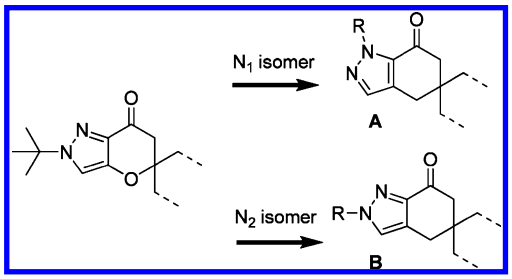
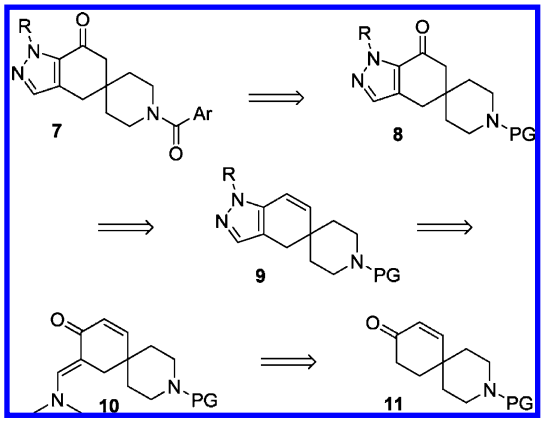




**Figure 2.** Desired regioisomeric pyrazole substitution.

regioselective condensation reactions using substituted hydrazines. Our retrosynthetic analysis to $N_1$ alkyl compounds is shown in Scheme 2, where analogs of **3**, such as **7**, would be accessed from spiroketone **8** via deprotection of the amine and a standard amide coupling. We believed that **8** could be accessed from olefin **9**, which was regarded as a key intermediate because the expected steric and electronic differentiation of the olefin carbons would allow for multiple methods for the olefin to ketone transformation to be explored.

**Scheme 2. Retrosynthesis of $N_1$ Substituted Oxodihydrospiroindazoles**

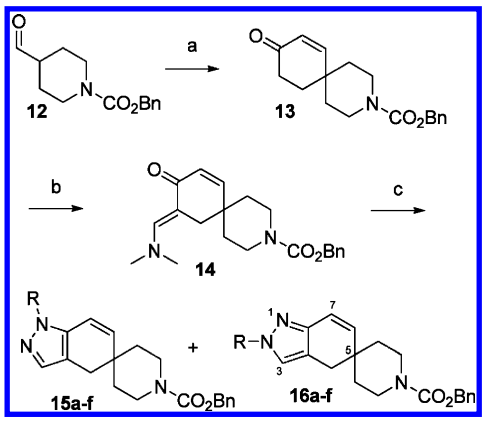



Olefin **9** would be derived from condensation of substituted hydrazines with enamine **10**. A logical precursor to **10** was spiroenone **11**, which could be obtained via Robinson annulation of a protected 4-formylpiperidine with methyl vinyl ketone (MVK).[5]

## RESULTS AND DISCUSSION

The synthesis of key olefin intermediate **15** is depicted in Scheme 3. Robinson annulation under basic conditions (KOH,

**Scheme 3. Synthesis of Key Olefin Intermediates**[a]




[a]Reaction conditions: (a) MVK, $PhCH_3$, 110 °C, *p*-TSA, Dean–Stark, 84%; (b) $HC(NMe_2)_3$ $PhCH_3$, 110 °C, quant; (c) R-$NHNH_2$.HCl, AcOH, EtOH, 90 °C, see Table 1 for yields.

EtOH)[8] using benzyl 4-formylpiperidine-1-carboxylate (**12**) and MVK produced enone **13** in only modest yield; however, use of *p*-TSA catalyzed acidic conditions with azeotropic removal of water produced **13** in high yield (84%).[9] Reaction of **13** with dimethylformamide dimethyl acetal (DMF-DMA) neat or in solution (DMF or $PhCH_3$) was unsuccessful; however, the more reactive reagent tris(dimethylamino)methane[10] (TDAM, 2 equiv) in refluxing $PhCH_3$ gave enamine **14** in quantitative yield. Formation of enamine **14** from enone **13** was also successful with Bredereck's reagent (*t*-butoxy bis(dimethylamino)methane) as the activated dimethylformamide source.[11]

**Achieving $N_1$ Regioselective Condensation.** Establishing high levels of regioselectivity in the condensation of alkyl hydrazines with enamine **14** was expected to be the key determinant of success for this synthetic plan. The condensation of **14** with various substituted hydrazine hydrochlorides was first examined in refluxing EtOH in presence of 2 equiv of AcOH.[12] The observed regioselectivity favoring the $N_1$ alkyl isomer **15** over the $N_2$ alkyl isomer **16** increased with the steric bulk of the alkyl group (Table 1), varying from a ratio of 1.2:1 (**15b**/**16b**) with methyl hydrazine hydrochloride to >50:1 (**15e**/**16e**) with *t*-butyl hydrazine hydrochloride (*t*-$BuNHNH_2$·HCl). This observed selectivity was consistent with literature reports[13] and confirmed by NOE experiments. Under these conditions, phenyl hydrazine hydrochloride also showed high selectivity for **15f** in 86% yield. Using *i*-propyl hydrazine hydrochloride (*i*-$PrNHNH_2$·HCl) alternate conditions were investigated to obtain higher regioselectivity (Table 1). Heating **14** and *i*-$PrNHNH_2$·HCl in EtOH in the presence of 2 equiv of AcOH resulted in a ratio of 11:1 **15d**/**16d** (entry 4). Heating in EtOH without AcOH did not affect the regioselectivity, returning a ratio of 11:1 (entry 7). Switching the solvent to $PhCH_3$ with 2 equiv of AcOH improved the selectivity to 22:1 **15d**/**16d** (entry 8) while refluxing in $PhCH_3$ alone without AcOH raised the level of selectivity to >30:1 **15d**/**16d** (entry 9). We were pleased to note an improvement in the regioselectivity of the condensation between methyl hydrazine hydrochloride and enamine **14** by 6-fold from 1.2:1 (entry 2) to 7:1 ratio of **15b**/**16b** (entry 10) by heating in $PhCH_3$ at reflux. At no time did we observe 1,4-addition to the enone with any of the alkyl hydrazines.


dx.doi.org/10.1021/jo202377g | J. Org. Chem. 2012, 77, 1497–1506

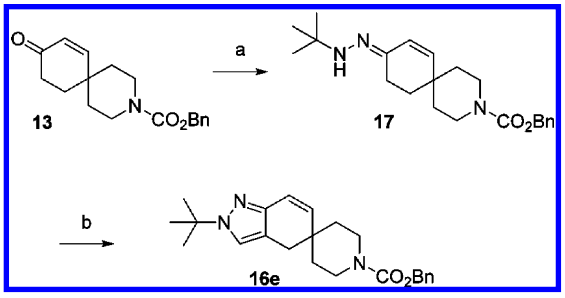
**Table 1. Substituent and Solvent Effects on Regiochemistry**

| entry | compound | R | solvent | AcOH (equiv) | yield of **15**/**16**[a] mixture (%) | ratio of **15**/**16**[b] | $C_7$ ppm[c] (**15**/**16**) |
|---|---|---|---|---|---|---|---|
| 1 | **15a** | H | EtOH | 2 | 87 | – | 6.59 |
| 2 | **15b**/**16b** | Me | EtOH | 2 | 89 | 1.2:1 | 6.38/6.54 |
| 3 | **15c**/**16c** | Et[d] | EtOH | 2 | 58 | 3.5:1 | 6.39/6.53 |
| 4 | **15d**/**16d** | *i*-Pr | EtOH | 2 | 77 | 11:1 | 6.43/6.57 |
| 5 | **15e**/**16e** | *t*-Bu | EtOH | 2 | 79 | >50:1 | 6.68/6.57 |
| 6 | **15f**/**16f** | Ph | EtOH | 2 | 86 | >30:1 | 6.53/6.66 |
| 7 | **15d**/**16d** | *i*-Pr | EtOH | – | 63 | 11:1 | 6.43/6.57 |
| 8 | **15d**/**16d** | *i*-Pr | $PhCH_3$ | 2 | 74 | 22:1 | 6.43/6.57 |
| 9 | **15d**/**16d** | *i*-Pr | $PhCH_3$ | – | 86 | >30:1 | 6.43/6.57 |
| 10 | **15b**/**16b** | Me | $PhCH_3$ | – | 62 | 7:1 | 6.38/6.54 |

[a]Typical reaction conditions (General method A): 1 equiv of **14**, 1.4 equiv of alkyl hydrazine HCl, 2 equiv of AcOH, EtOH, 2–18 h, reflux. [b]Ratio determined by NMR. [c]Shift (in ppm) of diagnostic doublet signal from olefin proton at $C_7$. [d]Ethyl hydrazine oxalate salt used in place of hydrochloride salt.

**Selective $N_2$ Alkyl Pyrazole Synthesis.** With a method to prepare $N_1$ substituted 1,4-dihydrospiroindazoles in hand, we turned our attention to the regioselective synthesis of the $N_2$ substituted analogs. The $N_2$ *t*-butyl derivative was targeted as a direct comparison with compound **3** to evaluate the effect of changing the ring oxygen to methylene. We hypothesized that the same key spiroenone **13** could be utilized to access the desired $N_2$ derivatives by condensing with an alkyl hydrazine first, creating a hydrazone, and attempting to close the pyrazole ring with a formic acid equivalent, effectively reversing the synthetic route used to prepare the $N_1$ isomers. Condensation of the spiroenone **13** with *t*-BuNHNH$_2$·HCl in refluxing EtOH provided hydrazone **17** in 70% yield. Installation of the pyrazole carbon atom was attempted with DMF-DMA,[14] TDAM and HC(OEt)$_3$ but attempts to cyclize to the pyrazole **16e** were unsuccessful and returned starting hydrazone. Inspired by a literature report from Prasad,[15] who reported that an $\alpha$-unsubstituted hydrazone can be condensed with Vilsmeier reagent to produce a pyrazole ring, we successfully reacted **17** with 3 equiv of Vilsmeier reagent (freshly prepared from $POCl_3$ in DMF at 0 °C) at 80 °C to deliver the desired **16e** in 65% yield (Scheme 4). We now had developed two

**Scheme 4. Regioselective Formation of $N_2$ *t*-Bu Pyrazole[a]**

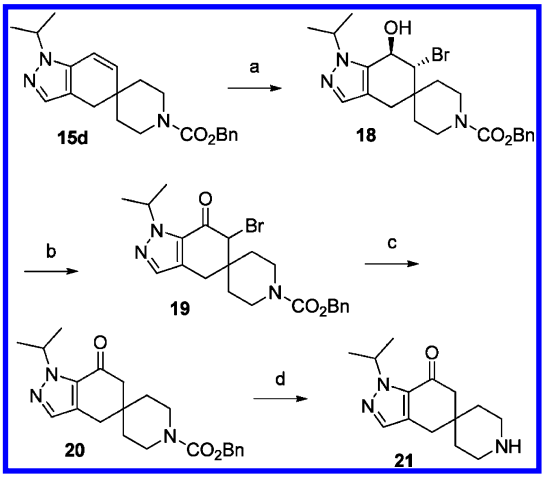



[a]Reaction conditions: (a) *t*-BuNHNH$_2$·HCl, EtOH, reflux, 70%; (b) $POCl_3$, DMF 0 °C, then **17**, 80 °C, 65%.

complementary synthetic routes designed to deliver either pyrazole isomer in a regioselective manner.

**Conversion of Olefin to Ketone.** At this point the carbon skeletons of both desired core structures were fully elaborated and conversion of the olefin to the desired ketone was the remaining functionalization to be completed. Initial attempts to oxidize the $N_1$-substituted olefin **15d** directly to ketone **20** via Wacker oxidation[16] were unsuccessful. In addition, olefin **15d** proved inert to various hydroboration/oxidation conditions (borane–THF,[17] 9-BBN[18] and Pd-catalyzed catecholborane[19]). Interestingly, Moorthy[20] reported that an olefin could be converted directly to an $\alpha$-bromoketone by reaction with *N*-bromosuccinimide (NBS) in the presence of DMSO and IBX; however, when applied to **15d**, the major product from this one pot reaction was racemic *trans*-bromohydrin **18** (Scheme 5).

**Scheme 5. Conversion of Olefin to Ketone[a]**




[a]Reaction conditions: (a) NBS, THF, $H_2O$, rt; (b) Jones' Reagent, acetone, 0 °C; (c) Zn dust, THF, $NH_4Cl_{(aq)}$, rt (61% for 3 steps); (d) 1-methyl-1,4-cyclohexadiene, 10% Pd/C (50% wet), 80 °C, then 1 N HCl/$Et_2O$, 95%.

Despite the lack of reactivity of **18** toward *in situ* oxidation by IBX the regioselective formation of bromohydrin **18** offered a very attractive way to access **20** through oxidation of olefin **15d**. Thus, treatment of **15d** with 1 equiv of NBS in THF–water (3:1) at room temperature provided **18** which was directly oxidized with Jones' reagent[21] to furnish $\alpha$-bromoketone **19**. Debromination with Zn dust in a biphasic mixture of THF/aqueous $NH_4Cl$ (1:1) delivered spiroketone **20** in 61% yield over 3 steps. This sequence from olefin **15d** to spiroketone **20** (Scheme 5) was performed at room temperature, each reaction taking no more than 1 h with purification necessary only after the final debromination step. Protecting group removal under transfer hydrogenation conditions (Pd/C, 1-methyl,1–4-cyclohexadiene) followed by salt formation gave desired amine-HCl


dx.doi.org/10.1021/jo202377g | J. Org. Chem. 2012, 77, 1497–1506

**21** in 95% yield. This route could also be successfully applied to the $N_2$ alkyl regioisomer (e.g., **16e**).

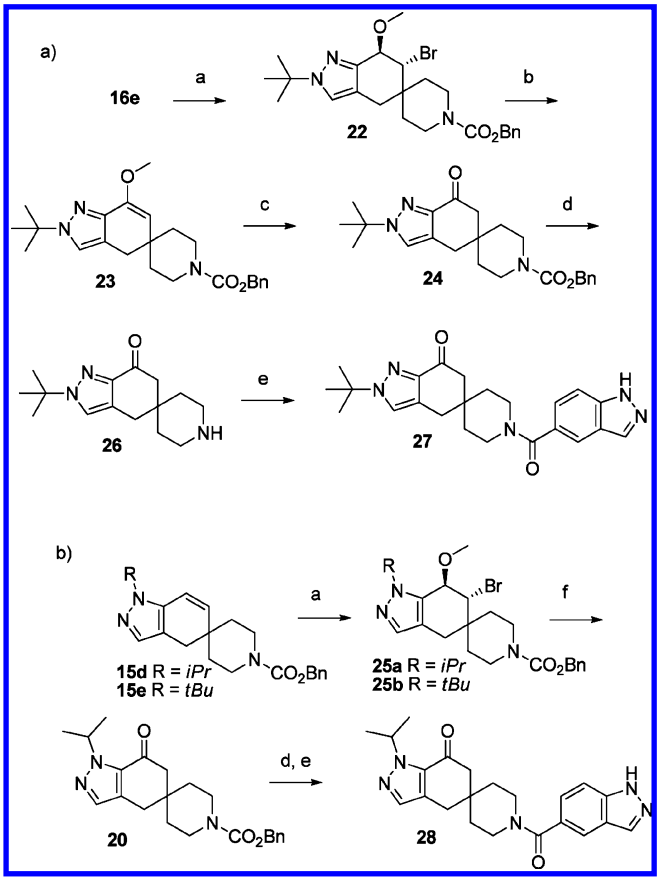
**Enabling Larger Scale Processes.** While the conversion of olefin to ketone was an efficient process using the three step NBS/Jones oxidation/Zn reduction route, we wished to avoid the hazards associated with the use of chromium-based oxidation reagents. Identification of a viable alternative to the Jones oxidation from **18** to **19** was not trivial, as many traditional green oxidation methods such as TEMPO/NaOCl returned **18**. Stoichiometric reagents such as $MnO_2$ and activated sulfoxide processes such as Swern and Parikh-Doering (pyridine-$SO_3$) also proved ineffective. The only oxidation process which proved successful was TPAP-NMO,[22] giving clean $\alpha$-bromoketone **19** in less than 1 h at room temperature.[23] Notably, the use of acetonitrile as solvent was critical to the success of this reaction. Even though we now had developed a quick and effective alternative process for converting the olefin **15d** to ketone **20**, the overall process involved three redox reactions to achieve a net one oxidation level change. Additionally, we were still producing Ru and Zn waste, and although catalytic, TPAP can be expensive on a larger scale. Thus, additional methods to convert the olefin **15d** to ketone **20** needed to be explored to develop a truly efficient route. Particularly, we preferred to complete the conversion from **15d** to **20** with just a single oxidative step.

Capitalizing on the oxidation state of bromohydrin **18**, we hypothesized that base-promoted elimination of HBr from **18** could lead directly to the desired ketone **20**. Usually, treatment of a *trans* bromohydrin with a base strong enough to effect an elimination reaction would deliver the epoxide[24] instead of the desired ketone **20**. To avoid epoxide formation, we recognized that we needed an *O*-alkyl bromohydrin.[25] Utilizing the $N_2$-substituted olefin **16e**, treatment with NBS in MeOH at room temperature delivered the desired *O*-methyl bromohydrin **22** within minutes in 83% yield. Several conditions were screened to promote the *syn*-elimination of HBr that would produce the desired enol ether.[26,27] It was found that treatment of **22** with potassium *tert*-butoxide (2 equiv) in THF at room temperature for 30 min gave enol ether **23** (not isolated), which upon quenching with 2 N HCl produced ketone **24** in 88% yield over two steps (Scheme 6a). Similar conditions were applied to $N_1$ substituted olefins **15d** and **15e**. Interestingly, in a classic demonstration of steric congestion, *O*-methyl bromohydrin **25a** required 18 h at room temperature or 1 h at 60 °C to complete the elimination to the enol ether before the acidic workup afforded **20**, while **25b** did not participate in the elimination reaction even under prolonged heating in THF at reflux (Scheme 6b).

Deprotection to amines **21** and **26** followed by amide formation with 1*H*-indazole-5-carboxylic acid delivered the final ACC inhibitors **27** and **28**, respectively.[28]

At this point, we had efficient and practical routes to both amines **21** and **26** with critical bond forming processes in five of the total six steps from *N*-protected 4-formyl piperidine through the amine deprotection. Our next step was to evaluate each of these steps to maximize yields and practicality on larger scale. For the synthesis of the $N_1$ *i*-propyl-substituted amine **21**, we discovered that a switch to BOC protected spiroenone **29**[29] offered multiple improvements. The CBZ protected spiroenone **13**, a thick, viscous oil, is difficult to handle whereas **29** is a free-flowing solid. In addition, use of BOC as a protecting group allows an acidic deprotection strategy, instead of a catalytic hydrogenation, directly producing the desired amine HCl salt.

**Scheme 6. Elimination Route to Ketone**[a]



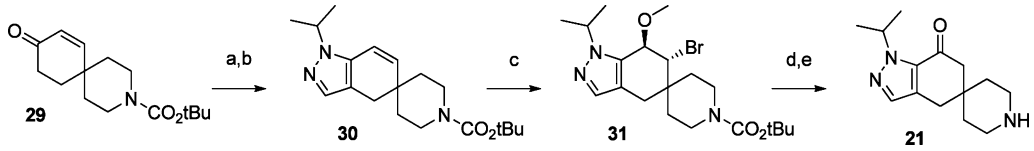

[a]Reaction conditions: (a) NBS, MeOH, $PhCH_3$, rt, 86% (b) KO*t*Bu, THF, rt; (c) 2 N HCl, THF, rt, 88% over 2 steps; (d) 1-methyl-1,4-cyclohexadiene, 10% Pd/C (50% wet), 80 °C, 95%; (e) 1*H*-indazole-5-carboxylic acid, T3P, $Et_3N$, DMF, rt, 72−75%; (f) (i) KOtBu, THF, 60 °C, 1 h or rt, 18 h; (ii) THF, 2 N HCl, rt, 89%.

This sequence also delivered high overall conversion with water-soluble byproducts. Bypassing chromatography and relying on aqueous workups allowed us to telescope the entire route from spiroenone **29** to the desired HCl salt of amine **21** (Scheme 7). Spiroenone **29** was converted to the intermediate enamine with TDAM in refluxing $PhCH_3$ and, after only an aqueous wash, taken directly into condensation with *i*-$PrNHNH_2$·HCl to form $N_1$-substituted pyrazole olefin **30**, again purification required only an aqueous wash. Treatment of compound **30** with NBS in MeOH delivered *O*-methyl bromohydrin **31**. Compound **31** was treated with potassium *tert*-butoxide in THF at 60 °C for 1 h followed by treatment with 1 N HCl, delivering the desired BOC-protected spiroketone. Deprotection was effected by HCl in EtOAc (AcCl/MeOH in EtOAc) and the HCl salt of **21** was collected by filtration in 93% yield over five telescoped steps from BOC-spiroenone **29** without chromatography on 50 g scale.

With amine **21** in hand in multigram quantities, we turned our attention to $N_2$ *t*-butyl amine **26**. In this case, the use of Vilsmeier reagent in the route to **26** prohibited the use of a BOC group as protection for the amine, and we focused on optimization of the route from CBZ-protected enone **13** (Schemes 3 and 5). On a large scale, the hydrazone **17** could be isolated by filtration as its HCl salt. The hydrazone was free-based and taken into the annulation reaction with freshly prepared Vilsmeier reagent ($POCl_3$/DMF). The crude olefin


dx.doi.org/10.1021/jo202377g | J. Org. Chem. 2012, 77, 1497−1506

**Scheme 7. Scale up of 21**[a]

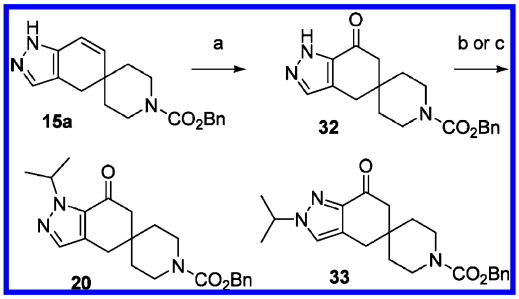



[a]Reaction conditions: (a) $HC(NMe_2)_3$ $PhCH_3$, 110 °C; (b) *i*-$PrNHNH_2$·HCl, MeOH, $PhCH_3$, 110 °C; (c) NBS, MeOH, $PhCH_3$, rt; (d) (i) KO*t*Bu, THF 60 °C; (ii) 1 N HCl, rt; (e) AcCl, MeOH, EtOAc, 93% overall yield (5 steps).

**16e** was converted to *O*-methyl bromohydrin **22** and then to the CBZ-protected spiroketone **24** through the previously described elimination route, at which point the material was subjected to chromatography. Spiroketone **24** was then deprotected via catalytic transfer hydrogenation; subsequent salt formation and recrystallization delivered 75 g of the pure HCl salt of amine **26**. Overall yield from enone **13** was 35%.

**Alternate Method for Selective Pyrazole Alkylation.** In parallel with our efforts to develop routes to deliver the $N_1$ and $N_2$ isomers with high regioselectivity, alkylation of the unsubstituted pyrazole was also examined.[30] We prepared spiroketone **32** from olefin **15a** via the NBS/Jones/Zn reduction route (Scheme 6). Alkylation of ketone **32** with 2-iodopropane in DMF with $K_2CO_3$ resulted in a 3.5:1 mixture of $N_1$ and $N_2$ *i*-propyl pyrazoles **20** and **33**. Alternatively, Mitsunobu alkylation[31] of spiroketone **32** with 2-propanol in THF with diisopropylazadicarboxylate (DIAD) and triphenyl phosphine ($Ph_3P$) delivered exclusively $N_1$-substituted ketone **20** in 91% yield (Scheme 8). We now had a second method

**Scheme 8. Selective Mitsunobu Alkylation at $N_1$**[a]




[a]Reaction conditions: (a) (i) NBS, THF, $H_2O$, rt; (ii) Jones' reagent, acetone, 0 °C; (iii) Zn dust, THF, $NH_4Cl_{(aq)}$, rt (58% for 3 steps); (b) $K_2CO_3$, 2-iodopropane, DMF, rt, 65% of 3.5:1 isomeric mixture; (c) 2-propanol, DIAD, $Ph_3P$, THF, rt, 91%.

available for delivering selectively alkylated pyrazoles, one from substituted hydrazines and another enabled for late stage diversification.

## CONCLUSION

We have described efficient and scalable routes to regiomeric oxo-dihydro spiroindazoles **21** and **26** and their subsequent conversion to **27** and **28** as ACC inhibitors. During this exploration, we have shown a methodology to form alkyl pyrazoles with complete regiocontrol. Selectivity in the condensation between a keto-enamine and substituted hydrazines was improved by use of $PhCH_3$ as solvent, giving nearly complete selectivity for the $N_1$ isomer. The complementary $N_2$ regioisomer was obtained by a reordering of the synthetic steps and closing the pyrazole with Vilsmeier reagent. These methods allowed us to access the desired oxo-dihydro spiroindazoles and thus ACC inhibitors **27** and **28**. A key finding that enabled the development of a process friendly scalable route was the use of NBS in MeOH to form an *O*-methyl bromohydrin intermediate, which upon elimination/enol ether hydrolysis allowed efficient access to a ketone intermediate in high yield, thereby removing one full redox cycle from the original synthetic route. This bromination/elimination sequence provides an alternative to traditional Wacker oxidation conditions without the need for metal catalysis and an oxygen atmosphere. The routes developed allowed synthesis of both amine **21** and amine **28** on a greater than a50 g scale with minimal purification steps.

## EXPERIMENTAL SECTION

**General Experimental Details.** Unless otherwise stated, all reactants, reagents and solvents were obtained from commercial sources and used without further purification. Data for $^1$H NMR spectra are reported relative to residual solvent signals (for $CDCl_3$, $\delta$H = 7.27 ppm; for DMSO-$d_6$, $\delta$H = 2.50 ppm) as follows: chemical shift ($\delta$ ppm), multiplicity, coupling constant (Hz) and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; spt, septet; m, multiplet; br s, broad singlet. Data for $^{13}$C NMR spectra are reported in terms of chemical shift ($\delta$ ppm) relative to residual solvent signals (for $CDCl_3$, $\delta$H = 77.0 ppm; for DMSO-$d_6$, $\delta$H = 39.5 ppm). Flash chromatography was carried out on either a Biotage SP purification system or a Combiflash Companion from Teledyne Isco; Biotage SNAP, KPsil or Redisep Rf silica columns were used. Except where otherwise noted, all reactions were run under an inert atmosphere of nitrogen gas using anhydrous solvents at room temperature (~23 °C). The terms "concentrated" and "evaporated" refer to the removal of solvent at reduced pressure on a rotary evaporator with a water bath temperature not exceeding 60 °C. Chloride ion determination was carried out by QTI, Whitehouse, NJ.

**Benzyl 9-Oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate (13).** To a solution of benzyl 4-formylpiperidine-1-carboxylate (**12**) (90 g, 363.9 mmol) in benzene (700 mL) in a 2 L 3 neck round-bottom flask fitted with a Dean–Stark trap was added *p*-TSA monohydrate (692 g, 36.4 mmol) and the mixture was heated to 70 °C. MVK (61.8 mL, 753 mmol) was added and the reaction mixture was heated at reflux for 24 h collecting expelled water in the trap. The reaction was cooled to ambient temperature and washed with saturated $NaHCO_3$(aq). The layers were separated and the organic layer was dried over $Na_2SO_4$, filtered and concentrated. The resultant dark-brown oil was purified by flash chromatography on silica gel, eluting with a gradient of 0–100% EtOAc/heptane to afford **13** (91.7 g, 84%) as a brown oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.29 (m, 5H), 6.80 (d, $J$ = 10.2 Hz, 1H), 5.96 (d, $J$ = 10.2 Hz, 1H), 5.14 (s, 2H), 3.69–3.59 (m, 2H), 3.50 (ddd, $J$ = 3.8, 8.3, 13.8 Hz, 2H), 2.51–2.41 (m, 2H), 1.97 (t, $J$ = 6.8 Hz, 2H), 1.74–1.63 (m, 2H), 1.62–1.52 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 198.9, 155.8, 155.2, 136.6, 128.5, 128.5, 128.0, 127.9, 67.2, 39.7, 34.8, 34.0, 33.4, 32.1; HR-MS calcd for $C_{18}H_{21}NO_3$ ($m/z$) $[M + H]^+$ 300.1594, found 300.1594.

**Benzyl 10-((Dimethylamino)methylene)-9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate (14).** To a solution of compound **13** (15.2 g, 51 mmol) in $PhCH_3$ (180 mL) was added tris(dimethylamino)methane (22.2 g, 153 mmol). The mixture was heated at reflux for 5 h and then allowed to cool to room temperature


dx.doi.org/10.1021/jo202377g | J. Org. Chem. 2012, 77, 1497–1506

overnight. The reaction solution was concentrated to provide **14** (18.0 g, >99%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.49 (s, 1H), 7.28−7.40 (m, 5H), 6.59 (d, $J$ = 10.1 Hz, 1H), 6.01 (d, $J$ = 10.1 Hz, 1H), 5.13 (s, 2H), 3.52−3.66 (m, 2H), 3.39−3.52 (m, 2H), 3.07 (s, 6H), 2.74 (s, 2H), 1.58−1.73 (m, 2H), 1.41−1.58 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 187.3, 155.6, 149.8, 149.6, 137.0, 130.8, 128.7, 128.2, 128.1, 99.9, 77.6, 77.3, 77.1, 67.3, 43.8, 40.4, 35.9, 35.4, 34.3; HR-MS calcd for $C_{21}H_{26}N_2O_3$ ($m/z$) [M + H]$^+$ 355.2016, found 355.2018.

**Benzyl 1,4-Dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (15a).** To a solution of compound **14** (9.13 g, 26.3 mmol) in EtOH (150 mL) was added hydrazine hydrate (1.53 mL, 31.5 mmol) and AcOH (1.50 mL, 26.3 mmol). The mixture was heated for 2 h at reflux then cooled to ambient temperature, concentrated and partitioned between EtOAc and water. The aqueous phase was extracted with additional EtOAc. The combined organic layers were washed with saturated $NaHCO_3$(aq) and brine, dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (100 g silica gel, 25−100% EtOAc/heptane gradient) to yield **15a** (7.42 g, 87%) as a pale-yellow foam. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.32 (br s, 1H), 7.40−7.30 (m, 5H), 7.28 (s, 1H), 6.58 (d, $J$ = 10.0 Hz, 1H), 5.97 (d, $J$ = 10.0 Hz, 1H), 5.15 (s, 2H), 3.64−3.54 (m, 2H), 3.53−3.43 (m, 2H), 2.65 (s, 2H), 1.69−1.58 (m, 2H), 1.56−1.44 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.3, 146.0, 137.2, 136.8, 128.4, 127.9, 127.8, 126.9, 118.8, 113.0, 67.0, 39.9, 35.6, 34.8, 30; HR-MS calcd for $C_{19}H_{21}N_3O_2$ ($m/z$) [M + H] $^+$ 324.1712, found 324.1711.

**Benzyl 1-Isopropyl-1,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (15d) and Benzyl 2-Isopropyl-1,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (16d). General Method A.** To a solution of compound **14** (1.18 g, 3.32 mmol) in EtOH (10 mL) was added AcOH (0.42 mL, 7.30 mmol) and *i*-PrNHNH$_2$·HCl (535 mg, 4.84 mmol). The reaction was heated at reflux for 18 h. The reaction was cooled to room temperature, diluted with EtOAc and washed with 0.5 N citric acid, water and brine. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated to obtain crude material, which was purified by flash chromatography (10−80% EtOAc/heptane gradient, 50 g silica) to yield 930 mg (77%) of an 11:1 mixture of **15d** and **16d**. For purposes of obtaining spectral data, the compounds were separated by preparative HPLC (250 × 21.2 mm 5 $\mu$ Phenomenex Cellulose-2, 5−100% EtOH/heptane gradient).

**15d.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.29 (m, 5H), 7.25 (s, 1H), 6.43 (dd, $J$ = 0.6, 10.0 Hz, 1H), 5.84 (d, $J$ = 10.1 Hz, 1H), 5.14 (s, 2H), 4.47 (spt, $J$ = 6.6 Hz, 1H), 3.62−3.45 (m, 4H), 2.62 (s, 2H), 1.68−1.59 (m, 2H), 1.57−1.51 (m, 2H), 1.49 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.6, 137.1, 136.5, 136.0, 135.8, 128.7, 128.2, 128.1, 114.8, 113.5, 67.2, 50.6, 40.2, 35.6, 35.3, 31.0, 22.8; HR-MS calcd for $C_{22}H_{27}N_3O_2$ ($m/z$) [M + H]$^+$ 366.2176, found 366.2181.

**16d.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.28 (m, 5H), 7.10 (s, 1H), 6.57 (d, $J$ = 10.0 Hz, 1H), 5.89 (d, $J$ = 10.0 Hz, 1H), 5.14 (s, 2H), 4.41 (spt, $J$ = 6.7 Hz, 1H), 3.65−3.55 (m, 2H), 3.52−3.42 (m, 2H), 2.60 (s, 2H), 1.72−1.61 (m, 2H), 1.53−1.51 (m, 2H), 1.49 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.3, 146.7, 136.9, 135.6, 128.4, 127.9, 127.8, 123.6, 119.9, 112.9, 67.0, 53.4, 40.0, 35.7, 34.5, 30.9, 23.0, 22.9; HR-MS calcd for $C_{22}H_{27}N_3O_2$ ($m/z$) [M + H]$^+$ 366.2176, found 366.2183.

*Alternate Condition 1.* Compound **14** (442 mg, 1.25 mmol) was treated according to General Method A, omitting AcOH to deliver an 11:1 mixture of compounds **15d** and **16d** (289 mg, 63%).

*Alternate Condition 2.* Compound **14** (442 mg, 1.25 mmol) was treated according to General Method A, with $PhCH_3$ as solvent to deliver a 22:1 mixture of compounds **15d** and **16d** (338 mg, 74%).

**General Method B.** Compound **14** (442 mg, 1.25 mmol) was treated according to General Method A, with $PhCH_3$ (without AcOH) as solvent to deliver $a$ > 30:1 mixture of compounds **15d** and **16d** (394 mg, 86%).

**Benzyl 1-Methyl-1,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (15b) and Benzyl 2-Methyl-2,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (16b).** The title compounds were prepared from compound **14** (1.18 g, 3.32 mmol) and methyl hydrazine hydrochloride according to General Method A to give a 1.2:1 mixture of **15b**/**16b** (0.99 g, 89%).

**15b.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.35 (m, 4H), 7.35−7.30 (m, 1H), 7.27 (s, 1H), 6.38 (d, $J$ = 10.0 Hz, 1H), 5.88 (d, $J$ = 9.8 Hz, 1H), 5.14 (s, 2H), 3.82 (s, 3H), 3.61−3.54 (m, 2H), 3.53−3.45 (m, 2H), 2.63 (s, 2H), 1.71−1.59 (m, 2H), 1.57−1.47 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 155.1, 137.0, 136.7, 136.5, 135.8, 128.3, 127.8, 127.7, 114.2, 113.2, 66.8, 39.7, 35.6, 35.1, 34.8, 30.7; HR-MS calcd for $C_{20}H_{23}N_3O_2$ ($m/z$) [M + H]$^+$ 338.1863, found 338.1861.

**16b.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42−7.29 (m, 5H), 6.54 (dd, $J$ = 0.6, 10.0 Hz, 1H), 5.90 (d, $J$ = 10.0 Hz, 1H), 5.14 (s, 2H), 3.83 (s, 2H), 3.66−3.54 (m, 2H), 3.53−3.39 (m, 2H), 2.62 (s, 2H), 1.69−1.59 (m, 2H), 1.55−1.44 (m, 2H) $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 155.1, 147.2, 136.7, 135.7, 128.2, 127.7, 127.6, 127.0, 119.6, 113.4, 66.7, 39.8, 38.4, 35.5, 34.3, 30.6; HR-MS calcd for $C_{20}H_{23}N_3O_2$ ($m/z$) [M + H]$^+$ 338.1863, found 338.1863.

Alternate preparation of **15b** and **16b**: Compound **14** (419 mg, 1.18 mmol) was treated with methyl hydrazine hydrochloride according to General Method B to yield a 7:1 mixture of compounds **15b** and **16b** (247 mg, 62%).

**Benzyl 1-ethyl-1,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (15c) and benzyl 2-ethyl-2,4-dihydrospiro-[indazole-5,4′-piperidine]-1′-carboxylate (16c).** The title compounds were prepared from compound **14** (1.18 g, 3.32 mmol) and ethyl hydrazine oxalate (300 mg, 4.99 mmol) according to General Method A to give a 3.5:1 mixture of **15c**/**16c** (675 mg, 58%).

**15c.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.29 (m, 5H), 7.23 (s, 1H), 6.39 (dd, $J$ = 0.6, 10.0 Hz, 1H), 5.85 (d, $J$ = 10.0 Hz, 1H), 5.14 (s, 2H), 4.11 (q, $J$ = 7.3 Hz, 2H), 3.67−3.40 (m, 4H), 2.63 (s, 2H), 1.68−1.58 (m, 2H), 1.58−1.48 (m, 2H), 1.42 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.6, 137.1, 136.7, 136.2, 128.7, 128.2, 128.1, 114.6, 113.6, 77.6, 77.2, 76.9, 67.3, 44.2, 40.1, 35.6, 35.2, 31.1, 16.0; HR-MS calcd for $C_{21}H_{25}N_3O_2$ ($m/z$) [M + H]$^+$ 352.2020, found 352.2020.

**16c.** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.27 (m, 5H), 7.05 (d, $J$ = 0.6 Hz, 1H), 6.53 (dd, $J$ = 10.0, 0.6 Hz, 1H), 5.87 (d, $J$ = 10.0 Hz, 1H), 5.12 (s, 2H), 4.07 (q, $J$ = 7.3 Hz, 2H), 3.56 (dd, $J$ = 6.7, 4.2 Hz, 2H), 3.50−3.36 (m, 2H), 2.58 (s, 2H), 1.66−1.58 (m, 2H), 1.48 (d, $J$ = 7.2 Hz, 2H), 1.44 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.6, 147.5, 137.1, 136.0, 128.7, 128.2, 128.0, 125.8, 120.1, 113.5, 77.6, 77.3, 76.9, 67.2, 47.0, 40.2, 34.8, 31.1, 15.9; HR-MS calcd for $C_{21}H_{25}N_3O_2$ ($m/z$) [M + H]$^+$ 352.2020, found 352.2022.

**Benzyl 1-Tert-butyl-1,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (15e).** The title compound was prepared from compound **14** (442 mg, 1.25 mmol) and *tert*-butyl hydrazine hydrochloride (218 mg, 1.75 mmol) according to General Method A to give $a$ > 50:1 mixture of **15e**/**16e** (376 mg, 79%).

$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39−7.35 (m, 4H), 7.33 (td, $J$ = 8.7, 4.5 Hz, 1H), 7.21 (s, 1H), 6.68 (d, $J$ = 10.2 Hz, 1H), 5.80 (d, $J$ = 10.0 Hz, 1H), 5.14 (s, 2H), 3.62−3.53 (m, 2H), 3.52−3.44 (m, 2H), 2.60 (s, 2H), 1.64−1.60 (m, 11H), 1.55−1.49 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.3, 136.8, 135.5, 135.3, 134.3, 128.4, 127.9, 127.8, 117.3, 115.3, 67.0, 59.4, 40.0, 35.2, 34.3, 30.9, 30.3; HR-MS calcd for $C_{23}H_{29}N_3O_2$ ($m/z$) [M + H]$^+$ 380.2333, found 380.2338.

**Benzyl 1-Phenyl-1,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (15f).** The title compound was prepared from compound **14** (424 mg, 1.20 mmol) and phenyl hydrazine hydrochloride (242 mg, 1.67 mmol) according to General Method A to give **15f** (412 mg, 86%). **16f** could not be isolated as a pure compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.55−7.45 (m, 5H), 7.40−7.30 (m, 6H), 6.54 (d, $J$ = 10.0 Hz, 1H), 5.92 (d, $J$ = 10.0 Hz, 1H), 5.16 (s, 2H), 3.69−3.59 (m, 2H), 3.56−3.46 (m, 2H), 2.71 (s, 2H), 1.69 (br s, 2H), 1.59 (br s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.3, 139.5, 138.1, 137.0, 136.8, 136.5, 129.2, 128.5, 128.0, 127.9, 127.1, 123.3, 115.7, 115.3, 67.1, 39.9, 35.4, 34.7, 31.0 HR-MS calcd for $C_{25}H_{25}N_3O_2$ ($m/z$) [M + H]$^+$ 400.2020, found 400.2022.

**Benzyl 2-Tert-butyl-2,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (16e).** Compound **13** (3.40 g, 11.4 mmol) was dissolved in EtOH (30 mL) and *tert*-butylhydrazine hydrochloride

(1.56 g, 12.5 mmol) was added. The mixture was heated at reflux for 18 h. The reaction was cooled to room temperature and concentrated under reduced pressure to yield **17** as a tan oil that solidified on standing.

To a suspension of compound **17** (4.21 g, 11.4 mmol) in dichloromethane (200 mL) was added $Et_3N$ (1.90 mL, 13.6 mmol) and the mixture was stirred for 30 min. The mixture was concentrated and the resultant oil taken up in methyl *t*-butyl ether (MTBE, 200 mL) and washed with water and brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. In a separate flask, DMF (50 mL) was cooled to 0 °C and phosphorus(V)oxychloride (3.12 mL, 34.1 mmol) was added dropwise over 30 min. The mixture was stirred at 0 °C for 30 min and the free base of hydrazone **17** was added as a solution in DMF (10 mL) in one portion. The resultant mixture was stirred at 80 °C for 18 h. The mixture was cooled to room temperature and diluted with MTBE (300 mL) and extracted with water. The combined aqueous phases were extracted with additional MTBE. The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (10−80% EtOAc/heptane gradient, 40 g silica gel) to yield **16e** (3.64 g, 85%) as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm 7.36−7.25 (m, 5H), 7.18 (s, 1H), 6.57 (d, $J$ = 10.0 Hz, 1H), 5.86 (d, $J$ = 10.0 Hz, 1H), 5.12 (s, 2H), 3.69−3.51 (m, 2H), 3.53−3.36 (m, 2H), 2.58 (s, 2H), 1.74−1.59 (m, 2H), 1.58−1.52 (m, 9H), 1.53−1.41 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.3, 146.6, 136.8, 135.4, 128.4, 127.9, 127.8, 127.7, 127.7, 122.9, 120.0, 112.6, 66.9, 57.9, 39.9, 35.8, 34.4, 30.9, 29.8; HR-MS calcd for $C_{23}H_{29}N_3O_2$ ($m/z$) $[M + H]^+$ 380.2333, found 380.2334.

**Benzyl 1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (20).** To a solution of compound **15d** (4.93 g, 13.49 mmol) in 3:1 THF/water (120 mL) was added freshly recrystallized NBS (2.63 g, 14.78 mmol). The clear orange solution was stirred for 15 min then diluted with EtOAc (300 mL) and washed with saturated $Na_2S_2O_3$(aq), 1 M NaOH, water and brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The resultant bromohydrin **18** was dissolved in acetone (80 mL) and cooled to 0 C. Jones' reagent (13.5 mL) was added dropwise and the reaction was stirred 1 h then cooled to 0 C. The reaction was neutralized slowly with saturated $NaHCO_3$(aq), filtered through Celite and rinsed with EtOAc. The biphasic filtrate was separated and the aqueous layer extracted with EtOAc. The combined organic phases were washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated to give bromoketone **19** as off-white foam. Compound **19** was dissolved in THF (50 mL) and saturated $NH_4Cl$(aq) (30 mL). The mixture was treated with Zn powder (2.13 g, 32.6 mmol) and stirred vigorously for 15 min. The reaction was diluted with EtOAc and the phases were separated and the organic layer washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (7−100% EtOAc/heptanes gradient, 100 g silica gel) to yield **20** (3.13 g, 61% over 3 steps) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.41−7.28 (m, 6H), 5.39 (spt, $J$ = 6.6 Hz, 1H), 5.13 (s, 2H), 3.59−3.51 (m, 2H), 3.50−3.43 (m, 2H), 2.75 (s, 2H), 2.54 (s, 2H), 1.55 (br. s., 4H), 1.46 (d, $J$ = 6.3 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 187.8, 155.5, 137.0, 136.5, 133.1, 128.7, 128.3, 128.1, 127.2, 77.5, 67.4, 52.7, 51.0, 40.0, 38.1, 35.4, 31.8, 22.6; HR-MS calcd for $C_{22}H_{27}N_3O_3$ ($m/z$) $[M + H]^+$ 382.2125, found 382.2131.

**1-Isopropyl-4,6-dihydrospiro[indazole-5,4′-piperidin]-7(1*H*)-one hydrochloride (21).** To a solution of compound **20** (416 mg, 1.09 mmol) in EtOAc (20 mL) was added 1-methyl-1,4-cyclohexadiene (1.26 mL, 10.9 mmol) and 10% Pd/C (80 mg, 50% wet). The resultant mixture was heated at reflux for 4 h. The reaction was cooled to room temperature and filtered through Celite and rinsed with EtOAc. The filtrate was treated with HCl (2 mL, 1 N in $Et_2O$) and concentrated to yield **21** (293 mg, 95%) as a white solid $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.89−8.67 (m, 2H), 7.47 (s, 1H), 5.27 (spt, $J$ = 6.6 Hz, 1H), 3.05 (br s, 4H), 2.79 (s, 2H), 2.62 (s, 2H), 1.71−1.60 (m, 4H), 1.36 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 187.1, 136.1, 132.1, 126.8, 51.5, 49.6, 38.8, 38.8, 36.2, 31.1, 30.1, 22.0, HR-MS calcd for $C_{14}H_{21}N_3O$ ($m/z$) $[M + H]^+$ 248.1757, found 248.1756.

**Benzyl 6-Bromo-2-*tert*-butyl-7-methoxy-2,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (22). General Method C.** To a solution of compound **16e** (414 mg, 1.09 mmol) in methanol (15 mL) was added freshly recrystallized NBS (194 mg, 1.09 mmol). The reaction was stirred for 30 min and concentrated. The resultant oil was taken up in EtOAc and washed with saturated $Na_2S_2O_3$(aq) and 0.5 M NaOH. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (24 g silica gel, 0−100% EtOAc/heptane gradient) to yield **22** (446 mg, 83%) as a clear oil.

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.34 (m, 4 H), 7.34−7.30 (m, 1 H), 7.27 (s, 1 H), 5.14 (s, 2 H), 4.76 (d, $J$ = 2.7 Hz, 1 H), 4.44 (d, $J$ = 2.2 Hz, 1 H), 3.81−3.72 (m, 1 H), 3.72−3.64 (m, 1 H), 3.59 (d, $J$ = 0.5 Hz, 3 H), 3.32 (t, $J$ = 9.5 Hz, 1 H), 3.24 (ddd, $J$ = 13.7, 9.7, 3.7 Hz, 1 H), 2.61 (s, 2 H), 1.87 (br. s., 1 H), 1.78−1.67 (m, 3 H), 1.60 (s, 9 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.3, 143.8, 136.8, 128.4, 127.9, 127.8, 122.9, 112.6, 78.6, 67.0, 60.7, 58.5, 57.6, 40.1, 39.6, 36.9, 33.1, 29.9, 26.7; HR-MS calcd for $C_{24}H_{32}BrN_3O_3$ ($m/z$) $[M + H]^+$ 490.1700, found 490.1701.

**Benzyl 2-*tert*-Butyl-7-oxo-2,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (24).** To a solution of compound **22** (289 mg, 0.59 mmol) in THF (15 mL) cooled to 0 °C was added dropwise potassium *tert*-butoxide (1.18 mL, 1 M in THF). The mixture was then warmed to room temperature and stirred for 30 min at which point 2 N HCl (5 mL) was added and stirring continued for 15 min. The reaction was diluted with water and extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (12 g silica, 10−100% EtOAc/heptane gradient) to yield **24** (206 mg, 88%) as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 (s, 1 H), 7.37−7.33 (m, 4 H), 7.33−7.29 (m, 1 H), 5.13 (s, 2 H), 3.53−3.47 (m, 4 H), 2.73 (s, 2 H), 2.59 (s, 0 H), 1.63 (s, 9 H), 1.60−1.52 (m, 0 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 191.8, 155.2, 145.0, 136.7, 128.4, 128.0, 127.8, 124.3, 123.4, 67.1, 60.2, 50.0, 39.7, 37.3, 35.3, 31.5, 29.8; HR-MS calcd for $C_{23}H_{29}N_3O_3$ ($m/z$) $[M + H]^+$ 396.2282, found 396.2287.

**2-*tert*-Butyl-4,6-dihydrospiro[indazole-5,4′-piperidin]-7(1*H*)-one hydrochloride (26).** To a solution of compound **24** (100 g, 253 mmol) in refluxing EtOAc (1 L) in a 2 L, 3-neck flask equipped with a condenser and mechanical stirrer and flushed with $N_2$ was added 20% $Pd(OH)_2$/C (7.10 g, 50% wet), and 1-methyl-1,4-cyclohexadiene (63.1 mL, 506 mmol). The reaction mixture was heated at reflux for 1 h. MeOH (300 mL) was added and the mixture was cooled to ∼40 °C and filtered through Celite. The filter cake was washed with a 1:1 mixture of MeOH/EtOAc (500 mL) and the combined filtrate was concentrated. The crude free base was taken up in MeOH (45 °C) and filtered. The filtrate was diluted with MeOH to a total volume of 300 mL in a 1 L, 3-neck flask, and stirred at 50 °C with a mechanical stirrer. Hydrogen chloride (72.1 mL, 4 N in dioxane) was added dropwise. Upon completion of the addition, the mixture was stirred at 50 °C for 40 min, then diluted with EtOH (500 mL) and the MeOH was removed by distillation. Additional EtOH was added to keep a constant volume and distillation continued until a ratio of ∼15:1 EtOH/MeOH (determined by $^1$H NMR) was reached. MeOH (20 mL) was added and the mixture was cooled slowly to room temperature and stirred for 18 h. The precipitated solids were collected by filtration, washed with EtOH and dried to yield **26** (75.3 g, 89%) as a white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.85 (br s, 2H), 7.83 (s, 1H), 3.04 (t, $J$ = 5.7 Hz, 4H), 2.76 (s, 2H), 2.56 (s, 2H), 1.67−1.59 (m, 4H), 1.53 (s, 9H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 190.75, 144.03, 125.69, 123.34, 59.61, 49.68, 38.98, 35.88, 31.43, 30.19, 29.36; HR-MS calcd for $C_{15}H_{23}N_3O$ ($m/z$) $[M + H]^+$ 262.1914, found 262.1914.

**Benzyl 6-Bromo-1-isopropyl-7-methoxy-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (25a).** The title compound was prepared from compound **15d** (465 mg, 1.27 mmol) and NBS (226 mg, 1.27 mmol) according to General Method C (563 mg, 93%) as a white solid. $^1$H NMR (400 MHz,


dx.doi.org/10.1021/jo202377g | J. Org. Chem. 2012, 77, 1497−1506

$CDCl_3$) $\delta$ 7.42−7.28 (m, 6H), 5.14 (s, 2H), 4.73 (d, $J$ = 1.8 Hz, 1H), 4.41 (s, 1H), 4.33 (spt, $J$ = 6.6 Hz, 1H), 3.87−3.74 (m, 1H), 3.70−3.60 (m, 1H), 3.55 (d, $J$ = 0.8 Hz, 3H), 3.36−3.26 (m, 1H), 3.22 (ddd, $J$ = 3.7, 9.8, 13.7 Hz, 1H), 2.69 (d, $J$ = 15.8 Hz, 1H), 2.50 (d, $J$ = 15.8 Hz, 1H), 1.82−1.63 (m, 4H), 1.50 (dd, $J$ = 6.8, 8.4 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.2, 136.7, 136.3, 132.4, 128.4, 128.0, 127.8, 113.9, 77.5, 67.0, 58.3, 57.3, 50.8, 40.1, 39.6, 37.1, 32.2, 26.1, 22.6, 22.5; HR-MS calcd for $C_{23}H_{30}BrN_3O_3$ ($m/z$) $[M + Na]^+$ 498.1363, 500.1345, found 498.1368, 500.1351.

**Benzyl 6-Bromo-1-*tert*-butyl-7-methoxy-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (25b).** The title compound was prepared from compound **15d** (324 mg, 0.85 mmol) and NBS (152 mg, 0.85 mmol) according to General Method C (359 mg, 85%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.40−7.31 (m, 5H), 7.31 (s, 1H), 5.14 (s, 2H), 4.90 (d, $J$ = 1.7 Hz, 1H), 4.47 (s, 1H), 3.92−3.77 (m, 1H), 3.75−3.66 (m, 1H), 3.52 (s, 3H), 3.27 (t, $J$ = 10.7 Hz, 1H), 3.23−3.16 (m, 1H), 2.78 (d, $J$ = 15.9 Hz, 1H), 2.49 (d, $J$ = 16.1 Hz, 1H), 1.92 (d, $J$ = 12.9 Hz, 1H), 1.82−1.74 (m, 1H), 1.71−1.64 (m, 2H), 1.63 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.2, 136.7, 135.4, 132.6, 128.4, 128.0, 127.8, 116.0, 78.6, 67.0, 61.0, 58.5, 56.3, 40.2, 39.7, 38.0, 35.9, 32.1, 29.8, 26.1; HR-MS calcd for $C_{24}H_{32}BrN_3O_3$ ($m/z$) $[M + H]^+$ 490.17, 492.1683, found 490.1708, 490.1691.

**2-*tert*-Butyl-1′-(1*H*-indazole-5-carbonyl)-4,6-dihydrospiro-[indazole-5,4′-piperidin]-7(2*H*)-one (27). General Method D.** To a solution of compound **26** (70 mg, 0.27 mmol) and 1*H*-indazole-5-carboxylic acid (48 mg, 0.30 mmol) was added $Et_3N$ (75 $\mu$L, 0.54 mmol) and T3P (0.31 mL, 50% in EtOAc). The resultant mixture was stirred for 4 h at room temperature. The mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromaotgraphy (12 g silica gel, 25−100% EtOAc/heptane gradient) to yield **27** (81 mg, 75%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.20−8.13 (m, 1H), 7.86 (s, 1H), 7.58−7.53 (m, 1H), 7.49−7.46 (m, 1H), 7.42 (s, 1H), 3.94−3.39 (m, 4H), 2.79 (s, 2H), 2.66 (s, 2H), 1.81−1.46 (m, 13H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 191.7, 170.6, 144.9, 135.1, 128.8, 126.4, 124.5, 123.3, 120.4, 110.2, 60.3, 50.0, 37.7, 35.6, 31.9, 31.7, 29.8, 18.6, 17.3; HR-MS calcd for $C_{23}H_{27}N_5O_2$ ($m/z$) $[M + H]^+$ 406.2238, found 406.2229.

**1′-(1*H*-indazole-5-carbonyl)-1-isopropyl-4,6-dihydrospiro-[indazole-5,4′-piperidin]-7(1H)-one (28).** The title compound was prepared from compound **21** (75 mg, 0.3 mmol) and 1*H*-indazole-5-carboxylic acid (54 mg, 0.33 mmol) according to General Method D to yield **28** (85 mg, 72%) as a white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 13.17 (s, 1 H), 8.08 (s, 1 H), 7.77 (s, 1 H), 7.52 (d, $J$ = 8.8 Hz, 1 H), 7.41 (s, 1 H), 7.32 (dd, $J$ = 1.4, 8.6 Hz, 1 H), 5.22 (spt, $J$ = 6.6 Hz, 1 H), 3.76−3.30 (m, 4 H), 2.76 (s, 2 H), 2.57 (s, 2 H), 1.46 (br s, 4 H), 1.31 (d, $J$ = 6.4 Hz, 6 H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 187.9, 169.3, 144.0, 139.8, 136.2, 134.2, 132.5, 128.2, 127.2, 125.2, 122.1, 119.7, 110.0, 51.6, 50.1, 38.5, 37.9, 30.4, 22.2; HR-MS calcd for $C_{22}H_{25}N_5O_2$ ($m/z$) $[M + H]^+$ 392.2081, found 392.2088.

**Large Scale Synthesis of 1-Isopropyl-4,6-dihydrospiro-[indazole-5,4′-piperidin]-7(1*H*)-one Hydrochloride (21).** To a solution of compound **29** (55.0 g, 207 mmol) in $PhCH_3$ (410 mL) was added tris(dimethylamino)methane (72 mL, 415 mmol) and the resultant mixture was heated at reflux for 4 h then allowed to stir at ambient temperature for 18 h. The mixture was concentrated and the resulting slurry was taken up in $PhCH_3$ (400 mL) and concentrated to a yellow solid. The yellow solid was taken up again in $PhCH_3$ (500 mL) and heated to 90 °C. To this solution was added *i*-$PrNHNH_2$·HCl (29.8 g, 269 mmol) as a solution in MeOH (75 mL) over 30 min. The mixture was heated at reflux for 4 h and allowed to cool to ambient temperature overnight. Most of the solvent was removed via distillation and the residue was cooled to room temperature and taken up in 10% citric acid(aq) (100 mL) and EtOAc (500 mL) and the layers were separated. The organic phase was washed with 10% citric acid(aq) (100 mL), water and brine. The combined aqueous washes were extracted with additional EtOAc (200 mL). The organic phases were combined and washed with water and brine. The solution was dried over $Na_2SO_4$, filtered and concentrated and the resultant oil was taken up in MeOH (500 mL) and concentrated (repeat 1x) to give olefin **30** as a thick orange oil. Compound **30** was taken up in MeOH (550 mL) in a 1 L flask placed in a water bath at ambient temperature. NBS (38.7 g, 217 mmol) was added in 2 portions (slight exotherm) and the mixture was stirred for 1 h. The reaction was quenched with $Na_2S_2O_3$(aq) (100 mL) and MeOH was evaporated. The resultant slurry was partitioned between EtOAc (100 mL), 2-methyltetrahydrofuran (2-MeTHF, 500 mL) and water (100 mL). The organic phase was washed with 1 N NaOH(aq) (2 × 80 mL), water (100 mL) and brine (100 mL). The combined aqueous layers were washed with 2-MeTHF (200 mL) and the organic phase was washed with water and brine (50 mL each). The organic extracts were combined, dried over $Na_2SO_4$, filtered and concentrated. The resultant oil was taken up in 2-MeTHF (300 mL) and $PhCH_3$ (100 mL) and concentrated (repeat 2×) to give *O*-methylbromohydrin **31** as a thick orange gum. Compound **31** was taken up in THF (300 mL) and potassium t-butoxide (414 mL, 1 M in THF) was added at room temperature via an addition funnel. The resultant dark red mixture was heated at 60 °C for 2 h then cooled to ambient temperature. Hydrochloric acid (1 N, 476 mL) was added over 20 min via an addition funnel and the mixture was stirred for 1 h and treated with EtOAc (500 mL). The phases were separated and the organic phase was washed with water. The combined aqueous phases were extracted with additional EtOAc. The combined organic layers were concentrated, taken up in a 1:1 mixture of THF/$PhCH_3$ and concentrated. The resultant orange oil was taken up in EtOAc (1 L) and treated with charcoal (25 g) for 40 min. The charcoal was removed by filtration through Celite, the filtercake washed with EtOAc (1.5 L) and the filtrate concentrated. The residue was taken up in EtOAc (660 mL) and MeOH (175 mL) and acetyl chloride (100 mL, 1.4 mol) was added dropwise over 20 min. The resultant mixture was stirred for 5 h. The precipitate was collected by filtration and dried in a vacuum oven to give compound **21** as a white solid (59.9 g, 93% overall yield; 1.8 equiv of HCl salt by Cl ion analysis). $^1$H and $^{13}$C spectra obtained were consistent with previous batches of compound **21**. For characterization purposes, a small amount of both compound **30** and compound **31** were isolated and purified and the data are listed below.

***tert*-Butyl-1-isopropyl-1,4-dihydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (30).** $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.26 (s, 1H), 6.43 (d, $J$ = 10.0 Hz, 1H), 5.85 (d, $J$ = 10.0 Hz, 1H), 4.48 (spt, $J$ = 6.6 Hz, 1H), 3.53−3.38 (m, 4H), 2.63 (s, 2H), 1.66−1.58 (m, 2H), 1.55−1.51 (m, 2H), 1.50 (d, $J$ = 6.8 Hz, 6H), 1.48 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 154.8, 136.5, 135.7, 135.6, 114.3, 113.3, 79.4, 50.3, 39.5, 35.4, 35.0, 30.7, 28.4, 22.6; HR-MS calcd for $C_{19}H_{29}N_3O_2$ ($m/z$) $[M + H]^+$ 332.2333, found 332.2339.

***tert*-Butyl-6-bromo-1-isopropyl-7-methoxy-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (31).** $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (s, 1H), 4.71 (d, $J$ = 1.7 Hz, 1H), 4.41 (s, 1H), 4.31 (spt, $J$ = 6.6 Hz, 1H), 3.72−3.62 (m, 1H), 3.55 (br s, 4H), 3.27−3.18 (m, 1H), 3.12 (ddd, $J$ = 13.7, 9.6, 3.5 Hz, 1H), 2.67 (d, $J$ = 15.9 Hz, 1H), 2.47 (d, $J$ = 15.9 Hz, 1H), 1.79−1.61 (m, 4H), 1.48 (dd, $J$ = 10.0, 6.6 Hz, 6H), 1.44 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 154.7, 136.3, 132.3, 114.0, 99.7, 79.5, 77.5, 58.4, 57.3, 50.7, 39.6, 37.2, 37.1, 32.3, 28.4, 26.1, 22.6, 22.5; HR-MS calcd for $C_{20}H_{32}BrN_3O_3$ ($m/z$) $[M + H]^+$ 442.1700, 444.1682, found 442.1710, 444.1692.

**Benzyl 7-Oxo-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (32).** To a solution of **15a** (608 mg, 1.88 mmol) in a 3:1 mixture of THF/water (20 mL) was added freshly recrystallized NBS (335 mg, 1.88 mmol). The reaction was stirred for 30 min and diluted with EtOAc and washed with saturated $Na_2S_2O_3$(aq). The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The resultant white solid was taken up in acetone (20 mL), cooled to 0 °C and treated with Jones' reagent (2.0 mL). The reaction was stirred for 1 h, neutralized with saturated $KH_2PO_4$(aq) and stirred for 20 min. The acetone was evaporated and the resultant slurry was diluted with water and extracted three times with EtOAc. The combined organic extracts were concentrated. The resultant tan oil was taken up in 1:1 THF/saturated $NH_4Cl$(aq)


dx.doi.org/10.1021/jo202377g | J. Org. Chem. 2012, 77, 1497−1506

(20 mL) and treated with Zn dust (369 mg, 5.64 mmol) with vigorous stirring for 30 min. The reaction was diluted with water and EtOAc and the layers separated. The organic phase was washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (24 g silica gel, 20−100% EtOAc/heptane gradient) to yield **32** (371 mg, 58%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.66 (s, 1H), 7.41−7.29 (m, 5H), 5.14 (s, 2H), 3.63−3.42 (m, 4H), 2.81 (s, 2H), 2.61 (s, 2H), 1.58 (br s, 4H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 155.2, 136.7, 128.5, 128.0, 128.0, 127.9, 67.1, 49.8, 39.7, 38.0, 35.2, 31.1; HR-MS calcd for $C_{19}H_{21}N_3O_3$ ($m/z$) $[M + H]^+$ 340.1656, found 340.1661.

**Benzyl 1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (20) and Benzyl 2-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (33) (Alkylation Method).** To a solution of compound **32** (100 mg, 0.30 mmol) in DMF (5 mL) was added $K_2CO_3$ (49 mg, 0.35 mmol) and 2-iodopropane (44 $\mu$L, 0.44 mmol). The mixture was stirred for 18 h. The reaction was diluted with MTBE and washed with water and brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (12 g silca gel, 0−100% EtOAc/heptane gradient) to yield compound **20** (57 mg, 51%) and compound **33** (16 mg, 14%). The spectra of **20** prepared via this method match those shown previously. Compound **33** spectroscopic data: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39−7.30 (m, 5H), 7.29 (s, 1H), 5.13 (s, 2H), 4.58 (spt, $J$ = 6.7 Hz, 1H), 3.50 (t, $J$ = 5.7 Hz, 4H), 2.73 (s, 2H), 2.59 (s, 2H), 1.62−1.51 (m, 10H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 191.6, 155.2, 145.1, 128.5, 128.0, 127.9, 125.1, 123.6, 67.1, 55.2, 50.0, 39.7, 37.4, 35.3, 31.4, 22.9; HR-MS calcd for $C_{22}H_{27}N_3O_3$ ($m/z$) $[M + H]^+$ 382.2125, found 382.2125.

**Benzyl 1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4′-piperidine]-1′-carboxylate (20) (Mitsunobu Alkylation Method).** To a solution of compound **32** (100 mg, 0.30 mmol) in THF (10 mL) was added 2-propanol (34 $\mu$L, 0.44 mmol), $Ph_3P$ (101 mg, 0.38 mmol) and DIAD (80 $\mu$L, 0.38 mmol) and the mixture was stirred for 18 h. The reaction was diluted with EtOAc and washed with water and brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude material was purified by flash chromatography (12 g silica gel, 0−100% EtOAc/heptane gradient) to yield compound **20** (102 mg, 91%) as a white solid. $^1$H and $^{13}$C spectra obtained were consistent with previous batches of compound **20**.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1$H and $^{13}$C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*Scott.W.Bagley@Pfizer.com


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Aaron Smith for helpful discussions, Kathleen Farley for NMR assistance, as well as James Bradow and Qi Yan for analytical and separation services. We are grateful to Bridge Organics Co., SynCom BV and WuXi AppTec, Inc. for resynthesis. In addition, we thank Bill Esler, Suvi Orr and Vincent Mascitti for their help with the manuscript.

## ■ REFERENCES


(1) Savage, D. B.; Petersen, K. F.; Shulman, G. I. *Physiol. Rev.* **2007**, *87*, 507−520.

(2) Saggerson, D. *Annu. Rev. Nutr.* **2008**, *28*, 253−272.

(3) Harwood, H. J. Jr.; Petras, S. F.; Shelly, L. D.; Zaccaro, L. M.; Perry, D. A.; Makowski, M. R.; Hargrove, D. M.; Martin, K. A.; Tracey, W. R.; Chapman, J. G.; Magee, W. P.; Dalvie, D. K.; Soliman, V. F.; Martin, W. H.; Mularski, C. J.; Eisenbeis, S. A. *J. Biol. Chem.* **2003**, *278*, 37099−37111.

(4) (a) Corbett, J. W.; Freeman-Cook, K. D.; Elliot, R.; Vajdos, F.; Rajamohan, F.; Kohls, D.; Marr, E.; Zhang, H.; Tong, L.; Tu, M.; Murdande, S.; Doran, S. D.; Houser, J. A.; Song, W.; Jones, C. J.; Coffey, S. B.; Buzon, L.; Minich, M. L.; Dirico, K. J.; Tapley, S.; McPherson, R. K.; Sugarman, E.; Harwood, H. J. Jr.; Esler, W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2383. (b) Corbett, J. W.; Elliott, R. L.; Bell, A. Spiroketone acetyl-CoA carboxylase inhibitors. WO08065508; 2008.

(5) For a recent review see: Corbett, J. W. *Expert Opin. Ther. Pat.* **2009**, *19*, 943−956.

(6) Freeman-Cook, K. D.; Amor, P.; Bader, S.; Buzon, L. M.; Coffey, S. B.; Corbett, J. W.; Dirico, K. J.; Doran, S. D.; Elliott, R. L.; Esler, W; Guzman-Perez, A.; Henegar, K. E.; Houser, J. A.; Jones, C. S.; Limberakis, C; Loomis, K.; McPherson, K.; Murdande, S.; Nelson, K. L.; Phillion, D.; Pierce, B. S.; Song, W.; Sugarman, E.; Tapley, S.; Tu, M.; Zhao, Z. *J. Med. Chem.* **2011**, DOI: 10.1021/jm201503u.

(7) Synthesis of spirochromanone and spirotetralone structures have been reported: (a) Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. *Tetrahedron* **2009**, *65*, 5161−5167. (b) Claremon, D. A.; Ponticello, G. S.; Selnick, H. G. Spirocycles useful as Class III antiarrhythmic agents. U.S. Patent 5,439,914, August 8, 1995.

(8) Pandey, A.; Seroogy, J.; Volkots, D.; Smyth, M. S.; Rose, J.; Mehrotra, M. M.; Heath, J.; Ruhter, G.; Schotten, T.; Scarborough, R. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1293−1296.

(9) Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, *52*, 4995−4996.

(10) (a) Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976**, 4459. (b) Bredereck, H.; Effenberger, F.; Brendle, T. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 132. (c) Bredereck, H.; Effenberger, F.; Brendle, T.; Muffler, H. *Chem. Ber.* **1968**, *101*, 1885.

(11) Bredereck, H.; Simchen, G.; Hoffmann, H.; Horn, P.; Wahl, R. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 356−357.

(12) (a) Menozzi, G.; Mosti, L.; Schenone, P. *J. Heterocycl. Chem.* **1984**, *21*, 1437−1440. (b) Molteni, V.; Hamilton, M. M.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. *Synthesis* **2002**, *12*, 1669−1674.

(13) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984−7034.

(14) Kennedy, L. J. *Synlett* **2008**, *4*, 600−604.

(15) Xu, D. D.; Lee, G. T.; Jiang, X.; Prasad, K.; Repic, O.; Blacklock, T. J. *J. Heterocycl. Chem.* **2005**, *42*, 131−135.

(16) Tsuji, J.; Nagashima, H.; Hori, K. *Tetrahedron Lett.* **1982**, *23*, 2679−2682.

(17) Wu, H.; Bernard, D.; Chen, W.; Strahan, G. D.; Deschamps, J. R.; Parrish, D. A.; Lewis, J. W.; MacKerell, A. D. Jr.; Coop, A. *J. Org. Chem.* **2005**, *70*, 1907−1910.

(18) Cheney, D. L.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 3334−3347.

(19) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671−6679.

(20) Moorthy, J. N.; Senapati, K; Singhal, N. *Tetrahedron Lett.* **2009**, *50*, 2493−2496.

(21) Fillion, E.; Trepanier, V. E.; Mercier, L. G.; Remorova, A. A.; Carson, R. J. *Tetrahedron Lett.* **2005**, *46*, 1091−1094.

(22) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639−666.

(23) Yield for the NBS/TPAP oxidation/Zn reduction pathway was 60% (3 steps), comparable to the NBS/Jones oxidation/Zn reduction (61%, 3 steps).

(24) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005−5007.

(25) (a) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105−1108. (b) Gomez-Sanchez, E.; Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 8656−8670.

(26) Potassium *t*butoxide was the only reagent tested to show complete conversion within 60 min. All test reactions were run on a 25 mg scale in 0.5 mL THF at ambient temperature with 2 equiv of additive. Reagents tested are as follows: NaOH (1 M aq), $Cs_2CO_3$, NaH (60% susp), NaOMe, KOtBu (1 M THF), DBU, pyridine, LiHMDS (1 M THF), NaHMDS (1 M THF), KHMDS (0.5 M THF), $Ag_2O$, $FeCl_3$ and $AlCl_3$.

(27) We reasoned that the adjacent pyrazole would facilitate the elimination via an E1cb-type mechanism.

(28) hACC $IC_{50}$'s for compounds **3**, **27** and **28** are 10, 9.5 and 30 nM respectively. For assay conditions, see ref 6.

(29) Fröhlich, J.; Sauter, F.; Hametner, C.; Pfalz, M. *Arkivoc* **2009**, 298−308.

(30) (a) Ye, L.; Knapp, J. M.; Sangwung, P.; Fettinger, J. C.; Verkman, A. S.; Kurth, M. J. *J. Med. Chem.* **2010**, *53*, 3772−3781. (b) Zhang, J.-H.; Fan, C.-D.; Zhao, B.-X.; Shin, D.-S.; Dong, W.-L.; Xie, Y.-S.; Miao, J. Y. *Bioorg. Med. Chem.* **2008**, *16*, 10165−10171.

(31) Beria, I.; Ballinari, D.; Bertrand, J. A.; Borghi, D.; Bossi, R. T.; Brasca, M. G.; Cappella, P.; Caruso, M.; Ceccarelli, W.; Ciavolella, A.; Cristiani, C.; Croci, V.; De Ponti, A.; Fachin, G.; Ferguson, R. D.; Lansen, J.; Moll, J. K.; Pesenti, E.; Posteri, H.; Perego, R.; Rocchetti, M.; Storici, P.; Volpi, D.; Valsasina, B. *J. Med. Chem.* **2010**, *53*, 3532−3551.