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Stereoselective synthesis of 1,3-substituted tetrahydroisoquinolines through palladium-catalyzed three-component reaction

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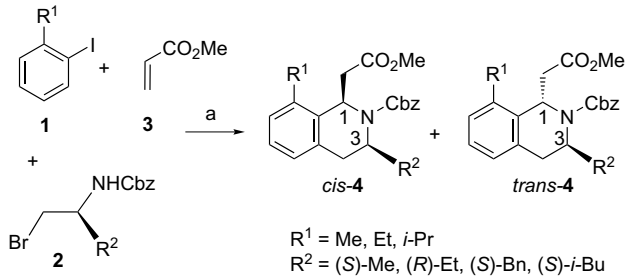
Abstract—Chiral 1,3-substituted 1,2,3,4-tetrahydroisoquinolines have been synthesized in acceptable yield and diastereoselectivity through a three component reaction, starting from aromatic halides, enantiopure bromoalkyl derivatives and methyl acrylate, under palladium catalysis.

1. Introduction

Multicomponent reactions (MCRs) are powerful tools for the rapid and efficient assembly of complex structures from simple starting materials with minimal production of waste.[1] For the synthesis of heterocycles, palladium-catalyzed MCRs turn out to be of great interest due to their functional group tolerability and the versatility of palladium in cross coupling reactions.[2]

The 1,2,3,4-tetrahydroisoquinoline nucleus has recently attracted significant attention, as it is the structural motif of many alkaloids.[3] In a preliminary communication, we disclosed a novel palladium-catalyzed three-component synthesis of 1-substituted tetrahydroisoquinolines **4** ($R^2 =$ H) (Scheme 1), assembled from a pool of simple molecules **1**, **2**, and **3** through the formation of two carbon–carbon and one carbon–nitrogen bonds in a single operation.[4] Herein, we explore the possibility of obtaining chiral tetrahydroisoquinolines **4** starting from enantiomerically pure Br-derivatives **2** (Scheme 1). The 1,3-substituted derivatives represent an important subclass of tetrahydroisoquinolines and only a few stereoselective syntheses have been reported so far.[3c–e] A key point in the synthesis of these compounds is the control of stereochemistry at the C-1 and C-3 carbon atoms. We wonder whether the use of enantiopure Br-derivatives **2** in the reaction outlined in Scheme 1 could address the formation of the new stereogenic center C-1 in **4**.[1b]



Scheme 1. Reagents and condition: (a) $Pd(OAc)_2$/tri-2-furylphosphine, norbornene, Cs_2CO_3, DMF, 80 °C.

2. Results and discussion

Compounds **2** can be easily prepared from the corresponding commercially available, enantiopure alcohols by OH/Br exchange (CBr_4, PPh_3 in THF). The reaction of **1**, **2**, and **3** in the presence of $Pd(OAc)_2$/tri-2-furylphosphine and norbornene as catalysts, Cs_2CO_3 as a base, in anhydrous DMF at 80 °C leads to **4** in acceptable yield and diastereoselectivity (Table 1).

Configurational assessment of each diastereomer has been carried out on compounds **4** ($R^2 =$ Et). Flash chromatography of the diastereomeric mixture of **4** gave the major diastereomer as a pure compound and the minor as an

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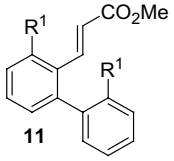
Table 1. Stereoselective palladium-catalyzed three-component synthesis of **4**[a]

Entry	R^1	R^2	Time (h)	**4**[b] (%)	*c*/*t* ratio[c]
1	Me	(*S*)-Me	15	49	78:22
2	Me	(*R*)-Et	9	56[d]	79:21[e]
3	Et	(*R*)-Et	15	52[f]	80:20
4	*i*-Pr	(*R*)-Et	15	60[f]	84:16
5	Me	(*S*)-Bn	12	48	76:24
6	Me	(*S*)-*i*-Bu	13	45	77:23

[a] Unless otherwise indicated, reactions were run with **1** (1 mol equiv), **2** (2 mol equiv), **3** (2 mol equiv), norbornene (2 mol equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (TFP) (20 mol %), Cs_2CO_3 (2 mol equiv) in DMF at 80 °C, [**1**] = 0.05 M.
[b] Yields after column chromatography.
[c] *cis*/*trans* diastereomeric ratio was determined by ^{1}H NMR and/or GC analysis of the crude.
[d] Compound **11** (R^1 = Me) was also isolated in 5% yield.



[e] With *t*-butyl acrylate a **4c**/**4t** ratio of 80:20 was obtained.
[f] With 4 mol equiv of norbornene.

80% enriched mixture. NMR studies allowed us to establish a *cis* relationship between the substituents bonded to C-1 and C-3 carbon atoms for the major diastereomer **4c**, and a *trans* relationship for the minor **4t** (Fig. 1). In the case of **4c**, NOE interactions between (a) H_a (2.60 ppm) and H_b (1.61 ppm), (b) H_a and the methyl group at 0.93 ppm were noteworthy. The assignment of the *trans* configuration to **4t** is supported by the observation of an NOE between H_a (2.70 ppm) and H-3 (4.00 ppm). Minimum energy geometries of the structures assigned to the products showed that in **4c** the heterocyclic ring adopts a boat-like conformation, wherein the C-1 and C-3 substituents are in a pseudo-axial position and the calculated distance between H_a and H_b is 2.19 Å. The C-1 and C-3 substituents of **4t** are pseudo-axial and equatorial, respectively, and the H_a–H_3 distance is 2.63 Å. In both cases the calculated distance between H_1 and H_3 is 4.46 Å, thus precluding any NOE effect.

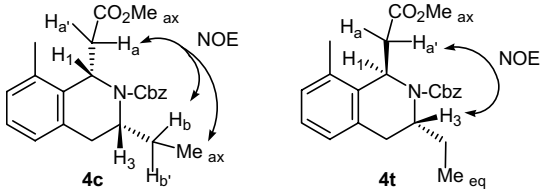
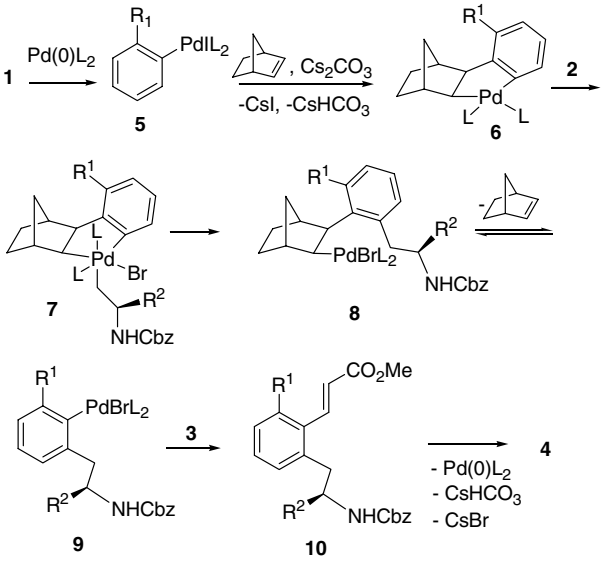


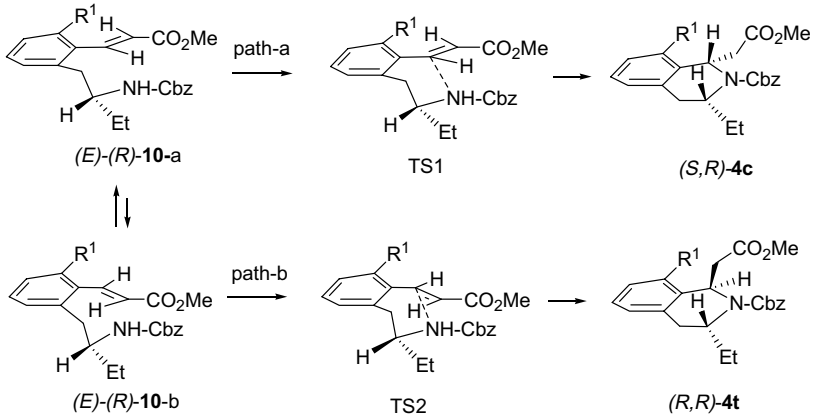
Figure 1. NOE interactions of **4c** and **4t** (R^1 = Me; R^2 = Et).

The three-component synthesis of **4** starts with a Pd-catalyzed aromatic substitution, made possible by sequential activation of two adjacent C–I and C–H bonds of an aromatic iodide, as discovered by Catellani.[5] The catalytic cycle begins with **1**, which oxidatively adds to palladium(0) affording **5** (Scheme 2, TFP as a ligand). Norbornene insertion and subsequent ring closure through C–H activation[6] give palladacycle **6**, $CsHCO_3$, and CsI. The aliphatic bromide **2** then reacts with **6** giving palladium(IV) metallacycle **7**. Reductive elimination forms **8**, which readily undergoes norbornene expulsion because of the steric hindrance of the two *ortho* alkyl substituents leading to **9**. Alkyl acrylate insertion completes the catalytic cycle with formation of the key-intermediate (*E*)-**10**, $CsHCO_3$, and CsBr. At this stage, **10** undergoes intramolecular aza-Michael addition, which determines the relative stereochemistry between substituents at positions 1 and 3 of **4**.[7]



Scheme 2. Proposed mechanism of **4**.

As shown in Scheme 3, compound **10** can assume α and β conformations. We hypothesize that the *cis*- and *trans*-isomers form through the less hindered nucleophilic attack of the nitrogen atom (–NHCbz) to the carbon–carbon double bond, according to path-α and -β, respectively.



Scheme 3. Proposed mechanism of the stereoselective intramolecular aza-Michael addition reaction.

AM1 calculations of the two diastereomeric transition states TS1 and TS2 showed a $\delta\Delta E^{\ddagger} = \Delta E^{\ddagger}_{trans} - \Delta E^{\ddagger}_{cis} =$ 5045 J/mol, which implies a predicted **4c**/**4t** ratio of 84:16. This finding agrees with the experimental results (Table 1). Apparently, the stereoselectivity is not affected by the encumbrance of R^1 and R^2substituents, the *cis*/*trans* ratio being nearly the same when varying their steric size.

The reaction of **1**, **2**, and **3**, run in DMF at 80 °C for a shorter time (1 h) gave intermediate **10** ($R^1 = Me$; $R^2 = Et$). Unexpectedly, treatment of **10** with Cs_2CO_3 (1 equiv) at 80 °C in DMF for 10 h in the absence of the catalyst gave an equimolar diastereomeric mixture of **4**. The involvement of palladium catalysis in the stereoselective carbon–nitrogen bond formation was ruled out after checking the stability of tetrahydroisoquinoline derivative **4c** under the aforementioned conditions. We observed that **4c** was transformed into a 1:1 mixture of *cis*/*trans* isomers. Apparently, the kinetically controlled product **4c** can equilibrate into **4t** through a base-catalyzed retro-Michael addition reaction. In the one-pot procedure, the cyclization occurs under less basic conditions ($CsHCO_3$) and C-1 epimerization is less favored. We also verified that diastereoselectivity is scarcely time-dependent. When prolonging the reaction time up to 20 h, the *cis*/*trans* ratio changed from 79:21 to 77:23.

Attempts to improve the stereoselectivity of the intramolecular aza-Michael reaction by running the cyclization of **10** at lower temperature and in the presence of a stronger base (kinetic control) did not produce better results. The crude containing **10** ($R^2 = Et$) was treated with *t*-BuOK (0.3 mol equiv) at room temperature. Under these conditions, cyclization occurred rapidly (5 min) giving **4** in a 62:38 diastereomeric ratio, which increased to 80:20 when the ring closure was carried out at −30 °C.

As shown in Scheme 2, compounds **4** result from a complex multistep mechanism. Tuning reagent and catalyst ratio is crucial to obtain satisfactory selectivity in terms of yield, as competitive side-reactions can occur and lead to several byproducts.[5] The crude of the reactions revealed the presence of compounds of type-**11** (Table 1, entry 2), as undesired products (**4**/**11** ratio ≅10:1, ^{1}H NMR analysis). Such compounds, isolated in one case (entry 2), originate from the reaction of the aromatic halide **1** with palladacycle **6**, according to a related catalytic sequence.[8] Two molar equivalents of **2** were needed[9] to counteract the competitive oxidative addition of **1** to **6**, thus minimizing the formation of **11**. With aryl iodides **1** bearing bulky groups in the *ortho* position (R^1 = Et, *i*-Pr), the reaction leads to **4** in low selectivity, when run under the conditions of Table 1. In both cases the use of 4 mol equiv of norbornene[10] improved yields significantly (20–25%), probably favoring the formation of palladacycle **6**.

3. Conclusion

In conclusion, we have developed a straightforward entry to optically active 1,3-substituted tetrahydroisoquinolines **4** in fair yield and reasonable diastereoselectivity through an asymmetric three-component reaction starting from **1**, **2**, and **3**. Our approach couples Pd-catalyzed alkyl/vinyl aromatic substitution and a stereoselective aza-Michael addition. This methodology is complementary to the reported ones.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercial suppliers and used without further purification. The palladium-catalyzed reactions were run under nitrogen using standard Schlenk and vacuum line techniques. Melting points are uncorrected. IR spectra were recorded with a Perkin–Elmer FT-IR 1725X spectrophotometer.

Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker 300-AMX spectrometer at 300 and 75 MHz, respectively. Phase sensitive ROESY spectra were measured on a 500 MHz with a mixing time t_m of 400 ms, while HMQC and HMBC were optimized for $^1J_{C-H} = 135$ Hz and $^{2,3}J_{C-H} = 8$ and 10 Hz, respectively.

4.2. Synthesis of enantiopure (1-alkyl-2-bromo)ethyl carbamic acid benzyl esters 2 (adapted from a reported procedure)[11]

A solution of tetrabromomethane (647 mg, 1.95 mmol) in anhydrous THF (5 mL) was added dropwise to a solution of PPh_3 (511 mg, 1.95 mmol) in THF (5 mL), kept at 0 °C. After the addition, the mixture was left at 0 °C under stirring for 15 min. Then, it was treated with a solution of the proper commercial *N*-Cbz protected 2-aminoalcohol (0.975 mmol) in THF (10 mL). The mixture was left under stirring at 0 °C for 10 min, then at rt for 2.0 h. The solid precipitate was filtered and washed with AcOEt (2×10 mL). The combined organic phases were washed with brine (70 mL), separated, and dried over Na_2SO_4. The crude residue was purified by chromatography on silica gel (eluent: hexane/AcOEt, 9:1).

4.2.1. Compound 2 (R^2 = (*S*)-Me). Yield 66%; white solid; mp 50–51 °C (hexane/AcOEt 9.5:0.5); $[\alpha]_D^{20} = -24.6$ (*c* 0.9, $CHCl_3$). IR (Nujol, cm^{-1}): 3341, 1686. ^1H NMR ($CDCl_3$): $\delta = 1.31$ (d, $J = 6.6$ Hz, 3H), 3.44 (dd, $J = 10.2$, 3.4 Hz, 1H), 3.56 (br dd, $J = 10.0$, 4.2 Hz, 1H), 4.02 (br s, 1H), 5.00–5.14 (m, 3H), 7.31–7.36 (m, 5H).^{13}C NMR ($CDCl_3$): $\delta = 19.1$, 39.1, 46.7, 66.6, 127.9, 128.0, 128.4, 136.2, 155.3. Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.45; H, 5.23; N, 5.15.

4.2.2. Compound 2 (R^2 = (*R*)-Et). Yield 62%; white solid; mp 60–62 °C (*i*Pr_2O); $[\alpha]_D^{20} = +28.6$ (*c* 1.2, $CHCl_3$). IR (Nujol, cm^{-1}): 3301, 1708, 1685. ^1H NMR ($CDCl_3$): $\delta =$ 0.97 (t, $J = 7.45$ Hz, 3H), 1.50–1.75 (m, 2H), 3.51–3.64 (m, 2H), 3.80 (br s, 1H), 4.90 (br s, 1H), 5.14 (br s, 2H), 7.33–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): $\delta = 10.2$, 26.0, 37.7, 52.2, 66.7, 127.9, 128.0, 128.4, 136.2, 155.7. Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.64; N, 4.89. Found: C, 50.29; H, 5.66; 4.91.

4.2.3. Compound 2 (R^2 = (*S*)-Bn). Yield 85%; white solid; mp 70 °C (*i*Pr_2O) (lit[12] 69–70 °C); $[\alpha]_D^{20} = -10.1$ (*c* 1.00, CH_2Cl_2).

4.2.4. Compound 2 (R^2 = (*S*)-*i*-Bu). Yield 50%; Dense oil; $[\alpha]_D^{20} = -23.8$ (*c* 2.1, CH_2Cl_2). IR (neat, cm^{-1}): 3322, 2957, 2932, 2869, 1699, 1530. ^1H NMR ($CDCl_3$): $\delta = 0.91$–0.95 (m, 6H), 1.40–1.46 (m, 2H), 1.60–1.70 (m, 1H), 3.45 (dd, $J = 10.4$, 3.4 Hz, 1H), 3.60 (dd, $J = 10.4$, 4.0 Hz, 1H), 3.95 (m, 1H), 4.80 (br d, $J = 8.4$ Hz, 1H), 5.10 (s, 2H), 7.30–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): $\delta = 22.2$, 22.6, 24.6, 38.7, 42.1, 49.0, 66.7, 127.9, 128.0, 128.4, 136.3, 155.6. Anal. Calcd for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42; N, 4.46. Found: C, 53.56; H, 6.46; N, 4.46.

4.3. Synthesis of 1,3-substituted tetrahydroisoquinolines 4

A Schlenk-type flask was charged under nitrogen with anhydrous Cs_2CO_3 (98 mg, 0.30 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), tri-2-furylphosphine (7.0 mg, 0.03 mmol), norbornene (28 mg, 0.30 mmol), and anhydrous DMF (1.0 mL). The mixture was stirred at rt for 10 min, then treated with **1** (0.15 mmol), **3** (26 mg, 27 μL, 0.30 mmol), and a solution of **2** (0.30 mmol) in anhydrous DMF (2.1 mL). The mixture was heated at 80 °C under stirring for the time reported in Table 1, then cooled to rt. After addition of a saturated aqueous *n*-Bu_4NCl (50 mL) and extraction with AcOEt (2×10 mL), the combined organic phases were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (eluent: hexane/AcOEt 8.5:1.5).

4.3.1. (1*R*,3*S*)-1-Methoxycarbonylmethyl-3,8-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid benzyl ester (4c, $R^1 = R^2$ = Me). Dense oil; $[\alpha]_D^{20} = +18.1$ (*c* 0.93, MeOH). IR (neat, cm^{-1}): 3030, 2950, 1739, 1695. ^1H NMR (DMSO-d_6, 80 °C): $\delta = 1.44$ (d, $J = 6.0$ Hz, 3H), 2.30 (s, 3H), 2.62 (dd, $J = 14.2$, 5.5 Hz, 1H), 2.81 (dd, $J = 14.2$, 9.6 Hz, 1H), 2.86 (dd, $J = 15.9$, 11.3 Hz, 1H), 3.05 (dd, $J = 15.9$, 7.13 Hz, 1H), 3.56 (s, 3H), 3.9 (m, 1H), 5.03–5.18 (m, 2H), 5.98 (dd, $J = 9.6$, 5.5 Hz, 1H), 7.06–7.13 (m, 3H), 7.36–7.38 (m, 5H). ^{13}C NMR (DMSO-d_6): $\delta = 17.8$, 22.2, 34.2, 38.8, 48.7, 49.8, 51.3, 66.4, 125.6, 127.3, 127.4, 127.8, 128.2, 128.3, 132.5, 134.5, 136.5, 136.8, 152.2, 170.4. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{22}H_{25}NO_4Na$, 390.16758; found, 390.16700.

4.3.2. (1*S*,3*R*)-3-Ethyl-1-methoxycarbonylmethyl-8-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid benzyl ester (4c, R^1 = Me; R^2 = Et). Dense oil; $[\alpha]_D^{20} = -0.8$ (*c* 1.16, MeOH). IR (neat, cm^{-1}): 3030, 2960, 2874, 1740, 1696. ^1H NMR (DMSO-d_6): $\delta = 0.93$ (t, $J = 7.5$ Hz, 3H, CH_2–CH_3), 1.61 (m, 1H, Hb), 1.96 (m, 1H, Hb′), 2.28 (s, 3H, 8-CH_3), 2.60 (dd, $J = 14.5$, 4.7 Hz, 1H, Ha), 2.78 (m, 1H, Ha′), 2.80 (m, 1H, H-4), 3.12 (dd, $J = 15.9$, 7.43 Hz, 1H, H-4′), 3.54 (s, 3H, O–CH_3), 3.75 (m, 1H, H-3), 5.07 (m, 2H, CH_2–Ph), 5.95 (dd, $J = 10.2$, 4.7 Hz, 1H, H-1), 7.04 (m, 2H, H-6, H_{para}), 7.05 (m, 2H, H_{meta}), 7.08 (m, 1H, H-5), 7.12 (m, 2H, H_{ortho}), 7.36 (m, 1H, H-7). ^{13}C NMR (DMSO-d_6): $\delta = 10.5$ (CH_2–CH_3), 18.3 (8-CH_3), 30.7 (CH_2–CH_3), 32.0 (C-4), 39.2 (CH_2–CO_2–), 50.3 (C-1), 51.9 (O–CH_3), 54.3 (C-3), 67.0 (CH_2–Ph), 126.4 (C-5), 127.8 (C-7), 127.9 (2C_{ortho}), 128.4 (2C_{meta}, 1C_{para}), 128.5 (C-6), 132.9 (C-8), 134.6 (C-4a), 137.1 (C_{ipso}), 137.3 (C-8a), 156.5 (N–CO), 170.9 (CO_2). HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{23}H_{27}NO_4Na$, 404.18323; found, 404.18357.

4.3.2.1. Characteristic NMR data of (1*R*,3*R*)-4t. ^1H NMR (DMSO-d_6, **4c**/**4t** = 20:80): $\delta = 0.67$ (t, $J = 7.0$ Hz, 3H, CH_2–CH_3), 1.39 (m, 2H, Hb, Hb′), 2.28 (s, 3H, 8-CH_3), 2.50 (dd, $J = 13.3$, 6.4 Hz, 1H, Ha), 2.70 (dd, $J = 13.3$, 6.4 Hz, 1H, Ha′), 2.80 (dd, $J = 15.5$, 2.0 Hz, 1H, H-4), 3.09 (dd, $J = 15.5$, 4.5 Hz, 1H, H-4′), 3.47 (s, 3H, O–CH_3), 4.00 (m, 1H, H-3), 5.14 (m, 2H, CH_2–Ph), 5.47 (t, $J = 6.4$ Hz, 1H, H-1), 7.04–7.37 (m, 8H). ^{13}C NMR (DMSO-d_6): $\delta = 10.5$ (CH_2–CH_3), 18.2 (8-CH_3), 30.7 (CH_2–CH_3), 32.0 (C-4), 39.2 (CH_2–CO_2–), 50.1 (C-1), 51.9 (O–CH_3), 53.8 (C-3), 67.1 (CH_2–Ph), 126.4 (C-5), 127.9 (2C_{ortho}), 128.4 (2C_{meta}), 134.6 (C-4a), 137.1 (C_{ipso}), 156.5 (N–CO), 170.9 (CO_2).

4.3.3. (1*S*,3*R*)-3,8-Ethyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid benzyl ester (4c, $R^1 = R^2$ = Et). Dense oil; $[\alpha]_D^{20} = -9.8$ (*c* 1.0, MeOH). IR (neat, cm^{-1}): 3032, 2964, 2875, 1741, 1695. ^1H NMR

(DMSO-d_6, 80 °C): $\delta = 0.97$ (t, $J = 7.4$ Hz, 3H), 1.16 (t, $J = 7.5$ Hz, 3H), 1.60–1.73 (m, 1H), 1.94–2.44 (m, 1H), 2.53–2.88 (m, 5H), 3.13 (dd, $J = 16.0$, 7.3 Hz, 1H), 3.58 (s, 3H), 3.72–3.83 (m, 1H), 5.05 (d, $J = 12.6$ Hz, 1H), 5.13 (d, $J = 12.6$ Hz, 1H), 6.05 (dd, $J = 12.0$, 4.9 Hz, 1H), 7.06–7.10 (m, 2H), 7.17 (t, $J = 7.5$ Hz, 1H), 7.34–7.37 (m, 5H). ^{13}C NMR (DMSO-d_6): $\delta = 10.2$, 15.5, 24.3, 30.0, 31.6, 39.0, 49.1, 51.4, 53.6, 66.5, 125.9, 126.6, 127.4, 127.7, 128.3, 134.5, 136.0, 136.7, 138.6, 156.1, 170.4. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{24}H_{29}NO_4Na$, 418.19888; found, 418.19855.

4.3.4. (1*S*,3*R*)-3-Ethyl-8-isopropyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid benzyl ester (4c, R^1 = *i*-Pr; R^2 = Et). Dense oil; $[\alpha]_D^{20} = -9.2$ (c 1.2, MeOH). IR (neat, cm^{-1}): 3031, 2962, 2929, 1739, 1695. ^{1}H NMR (DMSO-d_6, 80 °C): $\delta = 0.92$ (t, $J = 7.5$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.21 (d, $J = 6.8$ Hz, 3H), 1.59–1.75 (m, 1H), 1.95–2.07 (m, 1H), 2.55 (dd, $J = 15.8$, 7.5 Hz, 1H), 2.77–2.90 (m, 2H), 3.10–3.22 (m, 2H), 3.58 (s, 3H), 3.72–3.82 (m, 1H), 5.02–5.15 (m, 2H), 6.15 (dd, $J = 9.0$, 5.0 Hz, 1H), 7.06 (br d, 1H), 7.16–7.24 (m, 2H), 7.31–7.37 (m, 5H). ^{13}C NMR (DMSO-d_6): $\delta = 10.0$, 22.6, 24.7, 27.8, 30.7, 31.7, 39.3, 48.7, 51.3, 53.6, 66.5, 123.2, 125.7, 127.5, 127.6, 127.7, 128.2, 134.4, 135.7, 136.6, 143.1, 156.4, 170.3. HRMS (ESI) m/z: $[M+Na]^+$calcd for $C_{25}H_{31}NO_4Na$, 432.21453; found, 432.21378.

4.3.5. (1*R*,3*S*)-3-Benzyl-1-methoxycarbonylmethyl-8-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid benzyl ester (4c, R^1 = Me; R^2 = Bn). Dense oil; $[\alpha]_D^{20} = -40.9$ (c 1.00, MeOH). IR (neat, cm^{-1}): 3062, 3026, 2958, 2855, 1739, 1696. ^{1}H NMR (DMSO-d_6, 80 °C): $\delta = 2.30$ (s, 3H), 2.57 (dd, $J = 14.0$, 6.0 Hz, 1H), 2.74–2.95 (m, 4H), 3.36 (dd, $J = 13.0$, 3.1 Hz, 1H), 3.60 (s, 3H), 4.00 (m, 1H), 5.12 (d, $J = 12.0$ Hz, 1H), 5.15 (d, $J = 12.0$ Hz, 1H), 6.03 (dd, $J = 9.2$, 5.7 Hz, 1H), 6.95 (d, $J = 6.3$ Hz, 1H), 7.00–7.11 (m, 2H), 7.24–7.44 (m, 10H). ^{13}C NMR (DMSO-d_6): $\delta = 18.3$, 32.1, 39.2, 50.2, 51.9, 54.9, 67.4, 126.2, 126.8, 127.8, 128.4, 128.7, 128.9, 129.6, 133.1, 134.6, 137.2, 138.9, 155.6, 171.0. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{28}H_{29}NO_4Na$, 446.19888; found, 446.19892.

4.3.6. (1*R*,3*S*)-3-Isobutyl-1-methoxycarbonylmethyl-8-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid benzyl ester (4c, R^1 = Me; R^2 = *i*-Bu). Dense oil; $[\alpha]_D^{20} = +15.3$ (c 0.98, MeOH). IR (neat, cm^{-1}): 2954, 2870, 1740, 1696. ^{1}H NMR (DMSO-d_6, 80 °C): $\delta = 0.88$ (d, $J = 6.3$ Hz, 3H), 0.94 (d, $J = 6.3$ Hz, 3H), 1.50–1.60 (m, 1H), 1.75–1.85 (m, 2H), 2.3 (s, 3H), 2.62 (dd, $J = 14.4$, 5.4 Hz, 1H), 2.76–2.84 (m, 2H), 3.14 (dd, $J = 15.9$, 7.5 Hz, 1H), 3.57 (s, 3H), 3.50–4.04 (m, 1H), 5.03 (d, $J = 12.6$ Hz, 1H), 5.14 (d, $J = 12.6$ Hz, 1H), 5.98 (dd, $J = 9.6$, 5.4 Hz, 1H), 7.04–7.15 (m, 3H), 7.32–7.36 (m, 5 H). ^{13}C NMR (DMSO-d_6): $\delta = 17.7$, 20.9, 23.9, 24.1, 32.2, 38.4, 49.5, 50.3, 51.3, 66.5, 125.9, 127.1, 127.8, 128.0, 128.2, 132.5, 134.2, 136.8, 157.6, 170.4. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{31}NO_4Na$, 432.21453; found, 432.21404.

4.4. Computational details

The geometry of **4c** and **4t** was fully optimized at the AM1 level.[13] It was verified that structures **4c** and **4t** correspond to energy minima by the absence of negative eigenvalues of the Hessian matrix. The geometry of TS1 and TS2 was fully optimized at the AM1 level. Transition states TS1 and TS2 were confirmed by harmonic analysis, each one having a negative eigenvalue. All computations were carried out by the HYPERCHEM suite implemented in the Hyperchem 7.04 Professional package of programs, Hypercube, 2002.

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