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A comparison of two effective chiral auxiliaries—(2*R*)-bornane-10,2-sultam and (2*R*)-bornane-10,2-cyclohydrazide—using the [4+2] cycloaddition of cyclopentadiene to their *N*,*N*′-fumaroyl derivatives†

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Abstract

A correlation between the solvent polarity and the logarithm of the diastereoisomer ratio (dr) was found for the uncatalyzed [4+2] cycloaddition of cyclopentadiene to *N*,*N*′-fumaroyldi[(2*R*)-bornane-10,2-(2′-phenyl-pyrazol-3′-one)]. Using the Abboud–Abraham–Kamlet–Taft parameters, predictive values for this method resulted in an optimum diastereoisomeric excess (de) of more than 97% in hexane. Implications for the stereochemical course of the reaction as well as a comparison with the analogous (2*R*)-bornane-10,2-sultam auxiliary are discussed.

1. Introduction

We recently presented the complete π-facial selectivity observed in the $TiCl_4$-catalyzed [4+2] cycloadditions of cyclopentadiene to *N*-fumaroyl mono and bis[(2*R*)-bornane-10,2-sultam] (−)-**1a**,**b**.[1,2] Besides the influence of diverse Lewis acids, as well as applications using diverse dienes,[3] we also reported in detail the influence of the solvent polarity, ranging from the apolar CO_2 supercritical fluid to ionic liquid salts.[4] We observed that, in contrast to other auxiliaries,[5] a strong influence and a clear correlation between increasing solvent polarity and increasing

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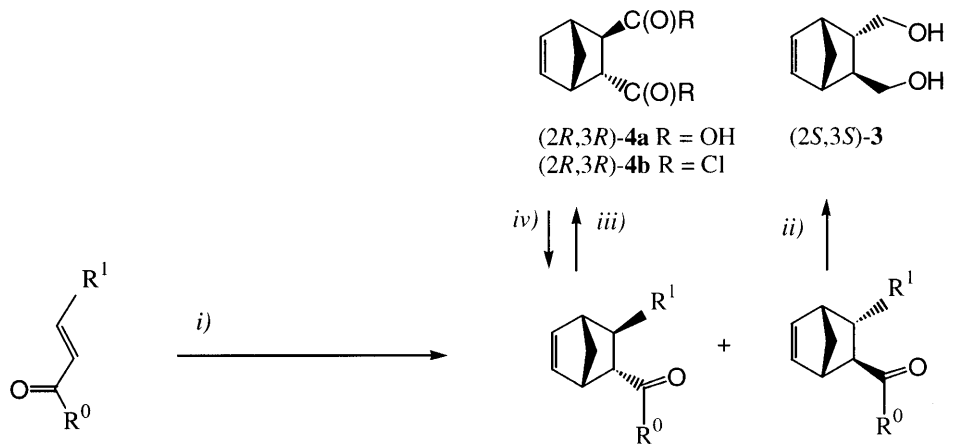
π-facial selectivity was found during the uncatalyzed cycloaddition of (−)-**1b** to cyclopentadiene. This was rationalized by the stabilization in polar solvents of the thermodynamically less favored *syn-s-cis* conformers and thus a more effective reactivity due to the cooperation of both steric and stereoelectronic effects for this class of dienophiles.[6] This effect is also reinforced by the additional stabilization by polar solvents of the C(α)-*re* transition states, exhibiting larger dipole moments in *syn* and *anti* conformations, compared to the corresponding C(α)-*si* attacks. We were thus particularly interested when Chen et al. recently reported the new *N*-acryloyl dipolarophile (−)-**1c**, which, according to these authors, is believed to react in the *syn-s-cis* conformation on the C(α)-*re* face.[7] Furthermore, these authors, depending on the solvent conditions used, also noticed an unexplained complete reversal of the inductive effect, during the Baylis–Hillman reaction on substrate (−)-**1c**.[8] This has prompted us to study the uncatalyzed cycloaddition of cyclopentadiene to the new dienophile (−)-**1d** in more detail.[9]

2. Results

The (+)-(2*R*)-bornane-10,2-cyclohydrazide chiral auxiliary was prepared from (+)-(1*S*)-ketopinic acid, according to the reported method.[8] The 2′-phenyl-pyrazol-3′-one was then



Scheme 1. (i) Solvent, 20°C, 24 h, 10.0 mol equiv. 1,3-cyclopentadiene; (ii) $NaBH_4$, $MeOH/H_2O$; (iii) LiOH, THF/H_2O; (iv) NaH, toluene, (2*R*)-bornane-10,2-cyclohydrazide-H

Table 1
Dependence of the diastereoselectivity of the cycloaddition (−)-**1d** to **2d** on the polarity and solvatochromic indexes

Solvent	Conv. (%)	De (%)	$E_T(30)$ (kcal/mol)	Log(dr)	π^*	α	β	δ	Calculated log(dr)	Residuals log(dr)
CF_3CH_2OH	85	56	59.8	0.550	0.73	1.51	0.00	0.0	0.575	−0.025
MeOH	85	63	55.4	0.644	0.60	0.98	0.66	0.0	0.650	−0.006
$MeNO_2$	94	88	46.3	1.195	0.85	0.22	0.06	0.0	1.184	0.010
MeCN	93	83	45.6	1.032	0.76	0.00	0.29	0.0	1.250	−0.218
DMSO	92	84	45.1	1.061	1.00	0.00	0.76	0.0	0.949	0.111
DMF	94	83	43.2	1.032	0.88	0.00	0.69	0.0	1.033	−0.001
CH_2Cl_2	91	90	40.7	1.279	0.82	0.13	0.10	0.5	1.249	0.030
$CHCl_3$	98	94	39.1	1.510	0.58	0.20	0.10	0.5	1.321	0.188
AcOEt	82	90	38.1	1.279	0.55	0.00	0.45	0.0	1.282	−0.003
THF	86	89	37.4	1.235	0.58	0.00	0.55	0.0	1.228	0.007
Toluene	96	92	33.9	1.380	0.54	0.00	0.11	1.0	1.461	−0.081
CCl_4	96	94	32.4	1.510	0.28	0.00	0.10	0.5	1.566	−0.057
Et_3N	96	91	32.1	1.327	0.14	0.00	0.71	0.0	1.365	−0.038
Hexane 0.0005 M	93	97	31.0	1.817	−0.04	0.00	0.00	0.0	1.736	0.082

deprotonated with NaH in toluene prior to addition of fumaroyl chloride to afford crystalline (−)-**1d** in 70% yield. It appears to be far less reactive than its camphorsultam analogue (−)-**1b**, (0.02 M, 20°C, 4.0 mol equiv. of cyclopentadiene, 18 h, full conversion[4]), since at higher concentration (0.05 M) and in the presence of an excess of cyclopentadiene (10.0 mol equiv.), the reaction was incomplete at 20°C, even after 24 h (Scheme 1).

The π-facial selectivity was measured directly by integration, in the 500 MHz ^{1}H NMR spectrum, of the olefinic signals of the diastereoisomeric mixture of cycloadducts **2d**, with a precision of ±2%. Indeed, the main stereoisomer shows signals at 5.92 and 6.34 ppm, while the minor one resonates at 6.00 and 6.21 ppm. The absolute configuration was determined by reduction of the main stereoisomer to the known diol (−)-(2*S*,3*S*)-**3**[10] {$NaBH_4$, 2.0 mol equiv., $MeOH/H_2O$ 3:1, 20°C, 1.5 h, 85% yield, SiO_2 hexane/Et_2O 7:3, $[\alpha]_D^{20} = -15.9$ ($c = 0.3$, $CHCl_3$)}. Alternatively, the minor stereoisomer was prepared by acylation of the chiral cyclohydrazide with enantiomerically pure bis-acid chloride (2*R*,3*R*)-**4b** (NaH, toluene), readily obtained [$(COCl)_2$, toluene, 80°C] after saponification ($LiOH{\cdot}7H_2O$, THF/H_2O 4:1) of the analogous enantiomerically pure major cycloadduct (2*R*,3*R*)-**2b**.[1]

After a rapid survey of common solvents such as toluene, THF, AcOEt, DMSO and MeCN, we rapidly concluded that the diastereoselectivity slightly diminished from 92 to 83% de on increasing the solvent polarity according to the Reichardt scale.[11] We then studied more systematically the complete range of solvent polarity from Et_3N (91% de) to CF_3CH_2OH (56% de) (see Table 1). As illustrated in Fig. 1, in contrast to the camphorsultam analogue, the logarithm of the diastereoisomer ratio (dr) decreased with increasing polarity. The optimum conversions (96–98%) and selectivities (94% de) were obtained in chlorinated solvents such as $CHCl_3$ or CCl_4.

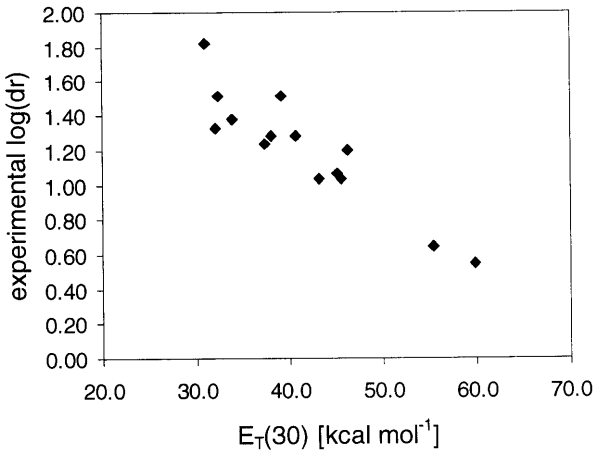


Figure 1. Diastereoselectivity of the uncatalyzed cycloaddition of (−)-**1d** to cyclopentadiene as a function of the solvent polarity as defined by the $E_T(30)$ values of Reichardt (dr = diastereoisomer ratio)

In hexane, the dienophile was practically insoluble and the conversion only reached 23% (82% de, reflecting here the solid/liquid interface interactions), while in that solvent under homogeneous high dilution conditions, more than 97% de were obtained after 93% conversion, according to the absence of the second diastereoisomer by ^{1}H NMR analysis. Finally, when the reaction was performed in neat cyclopentadiene, a selectivity of 97% de was observed after full conversion, while in refluxing toluene (83% conversion) the selectivity dropped to 61% de. Since

hydroxylic or some chlorinated solvents may activate the dienophile by forming a hydrogen bond, we then turned our attention towards a more generalized definition of the polarity as expressed by the multi-parameter Abboud–Abraham–Kamlet–Taft model,[12] where the log(dr) may be expressed as a linear correlation of diverse solvatochromic parameters as defined earlier.[4] The π^*, α, β, δ and square of Hildebrand indexes are characteristic of the solvent and have been recently compiled by Marcus et al.[13] and Chastrette et al.[14]

Based on 14 solvents, we found that the Hildebrand index was statistically not relevant and could be omitted without further alteration of the linear correlation ($r=0.96$ with this supplementary index, standard error = 0.119). Thus, a good correlation was found between the experimental and calculated diastereoselectivity (log(dr)), for the cycloaddition of (−)-**1d** to cyclopentadiene as shown in Fig. 2. A correlation coefficient of 0.96 was also found with a standard deviation of 0.113 when the equation was fitted with the following parameters.

$$\text{Log(dr)} = 1.717 - 0.460\pi^* + 0.037\delta - 0.534\alpha - 0.405\beta$$

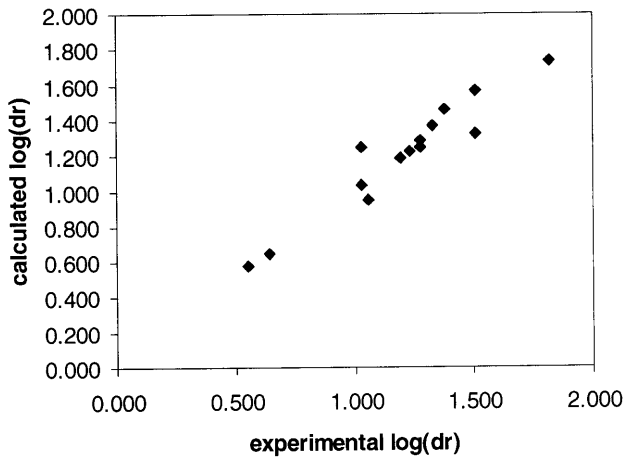


Figure 2. Experimental versus predicted diastereoselectivity of (−)-**1d** based on the Abboud–Abraham–Kamlet–Taft model (dr = diastereoisomer ratio)

3. Discussion

In summary, for the uncatalyzed cycloaddition to cyclopentadiene, dienophile (−)-**1d** exhibits opposite directing effects and relationships as compared to dienophile (−)-**1b**, as regards the diastereoselectivity obtained with respect to the solvent polarity.

Based on the X-ray analysis of (−)-**1c**, Chen et al. concluded that the C(α)-*re* sense of induction observed in their [3+2] cycloadditions resulted from the steric shielding of the top face by the C(8) Me group of the NPh/C=O *syn*-C=O/C=C-*s*-*cis* conformer.[7] This rationalization, initially suggested by Oppolzer in the case of the sultam auxiliary,[15] was later abandoned and replaced by a pure sterically masked C_2 symmetric concept described by Kim and Curran,[16] where the sense of induction is directed on the C(α)-*re* face by the C(2)–C(3) and *pseudo* axial S=O substituents in the *syn*- and *anti*-*s*-*cis* conformations, respectively. Although originally proposed,[17,18] but later rescinded[19] by Oppolzer and Curran, the stereoelectronic influence of the

nitrogen lone pair was only recently demonstrated by PM3 calculations, thus allowing us to tune the simple steric model by a supplementary matching or mismatching electronic factor in the *syn*- and *anti-s-cis* conformation, respectively.[6]

Comparison of the X-ray analyses of (–)-**1c**[7] or other derivatives[8] with the corresponding sultam analogue[18] is quite instructive. Indeed, beside the fact that the absolute structure parameters reported are not significant according to Ref. 20, as expressed for (–)-**1c** and another derivative[8] by an incorrect absolute configuration, five main features appear to be worthy of comment. First of all, similarly to the sultam auxiliary, the cyclohydrazide moiety possesses a pyramidalized N atom. This presumably results from the anomeric influence of the neighboring N lone pair, this latter atom preferring, in all instances, a *pseudo*-equatorial orientation of the Ph substituent. Secondly, this pyramidalization appears, as for the sultam derivatives,[6] to be dependent on the delocalization ability of the π-system. Thus, as expressed by the correlation observed between the N–N–C=O dihedral angle and the Δ*h*N values in Fig. 3, the N atom becomes more planar for a *syn*-periplanar orientation of the side chain carbonyl moiety. More surprisingly, based on the seven independent X-ray structures reported, and in contrast to the schemes depicted in the Chinese reports,[7,8] as well as to all the known sultam derivatives,[6] only one example shows a similar orientation of the N pyramidalization as in A (Scheme 2). In other words, for the cyclohydrazide derivatives, due to the C=O/Ph 1,5-interaction and depending on the side chain residue, the N lone pair is generally pointing downwards, *syn*-periplanar to the C(2)–H bond, as in conformer B.

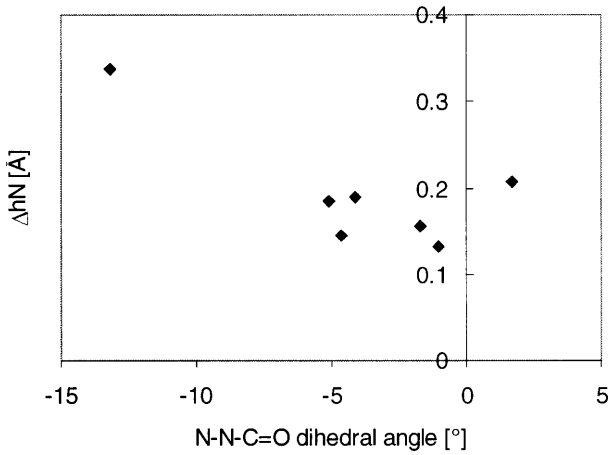
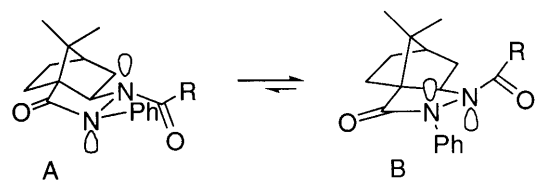


Figure 3. Dependence of the N pyramid's height related to the N–N–C=O dihedral angle



Scheme 2. Anomeric inversion of the N pyramidalization of (2*R*)-bornane-10,2-cyclohydrazide derivatives

In agreement with the generalized anomeric effect,[21] the most polarized N–C(2) bond is stabilized by the *anti*-periplanar C=O bond, thus electronically favoring the *syn-s-cis* conformer,

in direct contrast to the sultam analogue which prefers to align the C=O moiety *anti*-periplanar to the most polarized O_2S–N bond. Thus, in opposition to the steric approach, the N lone pair of the cyclohydrazide may favor, by its inverted orientation, electronic attack on the *syn-s-cis* C(α)-*si* and *anti-s-cis* C(α)-*re* faces.[6] Finally, the *pseudo*-equatorial aromatic ring is not parallel to the C(1)–C(7)–C(4) plane, but is tilted and mobile, and thus may protect either of the two faces, depending on the steric nature and trajectory of the incoming reagent.

The mobility of the Ph substituent, the *syn* conformation of the carbonyl moiety, as well as the possible inversion of the *N*-pyramidalization are the main stereo-differences with respect to the fixed SO_2 moiety of the sultam analogue. As a consequence, the sense of induction is difficult to predict in both *syn*- and *anti-s-cis* conformations, although the steric influence of the C(8) Me group appears to be more evident in conformers of type B. For this reason, we then turned our attention towards semi-empirical PM3 calculations.[22]

Earlier computations showed that, as a result of its convex nature, the thermodynamically most stable bis(*anti-s-cis*) conformer of (−)-**1b** possesses the smallest dipole moment, while the highly reactive bis(*syn-s-cis*) conformer, due to the vectorial addition of the SO_2 and C=O intrinsic dipoles, shows a more important global dipole moment.[4] The situation seems to be much more complicated with the auxiliary developed by Chen et al. Indeed, for this dienophile, we found four more stable co-planar conformers below the energy of the bis(*syn-s-cis*) conformer (−)-**1d** (see Table 2). Among them, the *anti-s-cis-s-trans-syn* or *anti-s-cis-s-cis-syn* conformers possess a higher dipole moment as compared to the bis *N*Ph/C=O *syn*, C=O/C=C *s-cis* conformer, more stabilized in apolar mediums. Interestingly, the energy differences between the transition states and the respective conformers of (−)-**1d** and cyclopentadiene at infinite separation, show that the main contributions do not originate from the thermodynamically more stable conformers (see Table 2). Indeed, the bis(*syn-s-cis*) and *anti-s-cis-s-cis-syn* conformers appear to kinetically drive the reaction, both C(α)-*si* approaches being the more relevant. In the case of the bis(*syn-s-cis*) conformer, the dipole moments of the transition states are smaller, thus a higher selectivity should be favored in apolar solvents, due to supplementary more discriminating competing participation on the C(α)-*si* face.

As emphasized earlier,[6] these calculations, performed in vacuum, take into account neither solvent effects nor entropic factors, and thus are only qualitative as shown by the too weak differences of energy found between both C(α)-*re* and -*si* approaches, as compared to the experimental results.

4. Conclusion

As a consequence of the cooperation of both prosthetic groups,[23] very high diastereoselectivity (>97% de, 90% yield) was obtained for the uncatalyzed [4+2] cycloaddition of (−)-**1d** to cyclopentadiene in apolar solvents such as hexane. A good linear correlation between the diastereoselectivity and the solvatochromic properties of the solvent was found, but in contrast to the sultam analog (−)-**1b**, dienophile (−)-**1d** exhibits opposite and increasing selectivity in apolar solvents. In contrast to the sultam analogues, the selectivity observed with cyclohydrazide derivatives of type (−)-**1d** is not straightforward to rationalize, due to the possible N pyramidal inversion and the mobility of the phenyl substituent. Furthermore, in contrast to the sultam derivatives, the carbonyl moiety prefers to adopt a *syn* conformation.

Table 2
PM3-calculated conformational energies, LUMO and dipole moments of (−)-**1d** as well as transitions state $\Delta\Delta H_{form}$ and dipole moments

Conformers of (−)-**1d**[a]	ΔH_{form} (kcal/mol)	LUMO (eV)	Dipole (D)	Cα-*re* attack $\Delta\Delta H$ (kcal/mol)	Dipole TS# (D)	Cα-*si* attack $\Delta\Delta H$ (kcal/mol)	Dipole TS# (D)
anti-s-trans-s-cis-syn	−20.8	−0.95	4.7	33.8	4.8	37.3	3.8
Bis(*syn-s-trans*)	−21.2	−1.19	2.6	35.1	0.9	35.7	4.4
Bis(*syn-s-cis*)	−21.6	−1.05	0.3	33.7	3.5	**33.1**	2.7
anti-s-cis-s-cis-syn	−21.9	−0.99	4.4	**33.0**	5.0	**32.9**	5.6
Bis(*anti-s-cis*)	−22.2	−0.83	1.8	33.9	3.8	34.5	0.3
syn-s-cis-s-trans-syn	−23.5	−1.14	3.3	34.2	3.1	34.7	3.5
anti-s-cis-s-trans-syn	−23.6	−1.04	4.5	36.9	4.5	37.3	5.6

[a] Although all the possible co-planar and pyramidal conformers were calculated, only those within 3.1 kcal/mol of the ground state conformation (−23.9 kcal/mol; >99.5 % of the populated conformers) are presented and taken into consideration for the TS calculations. For non-symmetric conformations, both *endo*/*exo* approaches were calculated, but only the lowest one is reported. The ΔH_{form} of cyclopentadiene is 31.7 kcal/mol.[6]

5. Experimental

General. See Ref. 24.

5.1. Dienophile (–)-*1d*

A soln of the chiral auxiliary[8] (2.3 g, 9.0 mmol; $[\alpha]_D^{20}=+56.5$ ($c=1.0$ $CHCl_3$)) in dry toluene (40 ml) was added dropwise to a suspension of NaH (0.9g, 22.5 mmol, 60% in min oil). After 30 min at rt, a soln of fumaroyl chloride (0.49 ml, 4.5 mmol) in toluene (2 ml) was added dropwise and the mixture was stirred for 3 days. The excess of NaH was quenched with H_2O. The mixture was extracted with CH_2Cl_2, the org. phases were dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on SiO_2 ($CHCl_3$/hexane 1:1 to 7:3) to afford crystalline (–)-**1d** in 70% yield. $R_f=0.24$ (hexane/AcOEt 3:2); mp: 150–153°C (AcOEt/hexane). $[\alpha]_D^{20}=-23.3$ ($c=1.0$, $CHCl_3$). IR (KBr): 2959, 2881, 1725, 1653, 1594, 1491, 1300, 1212, 1133, 755. ^{1}H NMR: 1.12 (s, 12H); 1.26–1.51 (m, 4H); 2.01 (dd, $J=13$, 8, 2H); 2.05–2.40 (m, 6H); 2.54 (brm, 2H); 4.16 (dd, $J=8$, 5, 2H); 7.04 (brs, 2H); 7.2–7.4 (m, 10H). ^{13}C NMR: 20.0 (2q), 20.2 (2q), 26.7 (2t), 28.3 (2t), 38.8 (2t), 46.6 (2d), 53.0 (2s), 59.2 (2s), 66.8 (2d), 121.5 (4d), 126.1 (2d), 128.6 (4d), 131.5 (2d), 138.0 (2s), 161.0 (2s), 170.0 (2s). HRMS: $C_{36}H_{40}O_4N_4$ 592.30734, calcd 592.30496. LRMS: 592 (6, $M^{+\bullet}$), 337 (19), 255 (100), 246 (7), 185 (6), 149 (9), 121 (11), 93 (12), 77 (17), 55 (8), 41 (11).

5.2. General procedure for the uncatalyzed cycloaddition

To a soln of (–)-(2*R*)-**1d** (50 mg, 0.1 mmol) in the appropriate solvent (2 ml), cyclopentadiene (82 μl, 1.0 mmol) was added dropwise. After 24 h at rt, the solvent and the excess of cyclopentadiene were evaporated under medium, then high vacuum. The crude cycloadduct **2d**, obtained after filtration through a short plug of SiO_2 (hexane/AcOEt 3:1) (99% yield), was submitted to ^{1}H NMR analysis for conversion and de determination. Pure samples for analysis were obtained after chromatography. Major diastereoisomer (+)-(2*S*,3*S*)-**2d**: $R_f=0.37$ (toluene/AcOEt 7:3); 0.40 (hexane/AcOEt 3:2); mp: 153–156°C (AcOEt/hexane); $[\alpha]_D^{20}=+124.3$ ($c=1.0$ $CHCl_3$); IR (KBr): 3009, 2962, 2881, 1726, 1689, 1596, 1492, 1377, 1300, 1271, 1204, 1134, 749. ^{1}H NMR: 0.99 (s, 6H); 1.05 (s, 6H); 1.20–1.35 (m, 5H); 1.6–2.2 (m, 9H); 2.63 (brm, 2H); 2.88 (m, 1H); 3.08 (brs, 1H); 3.22 (brs, 1H); 3.65 (brs, 1H); 3.88 (dd, $J=13$, 8, 2H); 5.98 (m, 1H); 6.34 (m, 1H); 7.06–7.14 (m, 2H); 7.20–7.33 (m, 8H). ^{13}C NMR: 19.8 (2q), 20.4 (2q), 26.6 (2t), 27.9 (2t), 39.4 (2t), 44.9 (d), 45.4 (d), 45.7 (2d), 47.3 (t), 49.0 (d), 50.5 (d), 54.8 (2s), 59.1 (2s), 65.6 (2d), 120.1 (4d), 125.2 (2d), 128.3 (4d), 133.6 (d), 137.3 (d), 138.8 (2s), 174.9 (2s), 175.7 (2s). HRMS: $C_{41}H_{46}O_4N_4$ 658.34924, calcd 658.35191. LRMS: 658 (4, $M^{+\bullet}$), 592 (6), 403 (77), 337 (100), 255 (85), 149 (31), 121 (34), 91 (45), 77 (39), 66 (44), 39 (35). Minor diastereoisomer (–)-(2*R*,3*R*)-**2d**: $R_f=0.39$ (toluene/AcOEt 7:3); 0.31 (hexane/AcOEt 3:2); mp: 204–207°C (AcOEt/hexane); $[\alpha]_D^{20}=-61.5$ ($c=1.0$ $CHCl_3$); IR(KBr): 2957, 2880, 1712, 1594, 1493, 1457, 1387, 1331, 1300, 1203, 1136, 1108, 1072, 1035, 915, 732, 693; ^{1}H NMR: 0.85 (m, 2H); 1.10 (s, 3H); 1.13 (s, 3H); 1.15 (s, 3H); 1.19 (s, 3H); 1.26 (m, 1H); 1.40 (m, 5H); 1.60 (m, 1H); 2.0 (m, 4H); 2.28 (m, 1H); 2.40 (m, 1H); 2.50 (m, 1H); 2.60 (m, 1H); 3.00 (brs, 1H); 3.20 (brs, 1H); 3.35 (dd, $J=13$, 8, 1H); 4.05 (dd, $J=19$, 13, 1H); 4.15 (dd, $J=19$, 13, 1H); 6.00 (dd, $J=14$, 8, 1H); 6.21 (m, 1H); 7.26 (m, 10H); ^{13}C NMR: 20.1 (q), 20.2 (2q), 20.3 (q), 26.8 (2t), 28.4 (2t), 40.1 (t), 40.4 (t), 45.8 (d), 46.1 (2d), 46.4 (d), 47.2 (d), 47.3 (t), 47.9 (d), 53.7 (s), 54.1 (s), 58.2 (2s), 66.1

(2d), 121.0 (2d), 121.1 (2d), 125.7 (2d), 128.4 (4d), 134.6 (d), 136.8 (d), 138.7 (2s), 158.0 (2s), 170.0 (s), 172.0 (s). HRMS: $C_{41}H_{46}O_4N_4Na$ 681.34110, calcd 681.34191. LRMS: 658 (5, $M^{+\bullet}$), 592 (5), 403 (75), 337 (100), 255 (85), 149 (30), 121 (35), 91 (45), 77 (40), 66 (45), 39 (35).

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