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Improved synthesis of *trans*-4-alkylcyclohexane carboxylic acids

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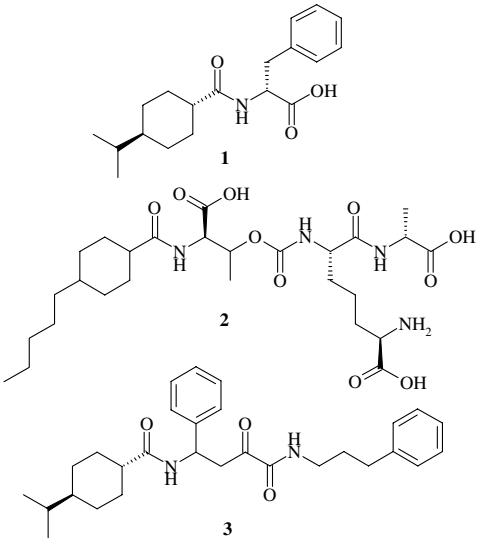
Abstract—Several stereomerically pure amino acid derivatives containing the N-terminal *trans*-4-alkylcyclohexanoyl fragment were obtained. Hydrogenation of 4-alkylbenzoic acids in the presence of a special Ru–Ni/C catalytic system and isomerization of the resulting mixture of *trans*- and *cis*-isomers of 4-alkylcyclohexanecarboxylic acids were used as the key steps. The stereomeric configuration of all compounds was confirmed by ^{1}H NMR spectroscopy. The compounds obtained possess a broad biological activity potential and are useful intermediates in the synthesis of stereomerically pure modified peptides.

1. Introduction

In recent years, stereochemically pure drugs have increasingly dominated the global pharmaceutical industry. A better understanding of the central role that chirality plays in biological processes has led to pharmaceuticals being developed as single stereoisomers. This need for single isomers has fueled the development of stereoselective reactions where chemists aim to synthesize compounds with their stereogenic centers of correct configuration, rather than as mixtures of stereoisomers that must be separated later.[1]



Due to the fact that the physiological activity of amino acids and peptides strongly depends on the configuration of their stereogenic centers, stereomerically pure peptides and peptidomimetics have been the subject of considerable interest. Many synthetic peptidomimetics have been described as potent and selective ligands to therapeutically significant protein biotargets.[2] From this point of view, there is considerable interest in synthesizing modified amino acids bearing N- or C-terminal stereomerically pure non-natural fragments. Such fragments can improve the pharmacological profile of potential therapeutic agents. In particular, synthetic peptidomimetics containing the N-terminal 4-alkylcyclohexanoyl fragment were reported as physiologically active agents. Probably the best known compound is the antidiabetic drug Nateglinide **1**, which represents a final generation of orally active modulators of insulin secretion with improved pharmacokinetics and reduced toxicity.[3] Both the pharmacokinetics and pharmacodynamics of Nateglinide strongly depend on the stereoconfiguration of the cyclohexane ring: only the *trans*-isomer possesses pharmacological activity. Among other physiologically active peptidomimetics containing the N-terminal 4-alkylcyclohexanoyl moiety, compound **2**[4] was described as a potential oncolytic, and compound **3**[5] was reported as an agent for the treatment of osteoporosis. A series of 4-alkylcyclohexanoyl acids and their amino acid

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derivatives has been synthesized, and their biological activity and toxicity were studied.[6]

In this work, we have developed a novel synthetic approach to structures containing *trans*-4-alkylcyclohexane and α-amino acid fragments. The approach is based on an efficient hydrogenation of 4-alkylbenzoic acids in the presence of a heterogeneous ruthenium–nickel catalyst followed by alkali-mediated isomerization of the mixture of *trans*- and *cis*-isomers of 4-alkylcyclohexanecarboxylic acids. It permits the convenient synthesis and separation of *trans*-4-alkylcyclohexanecarboxylic acids, which represent useful intermediates for introduction of the *trans*-4-alkylcyclohexane moiety into synthetic and natural molecules.

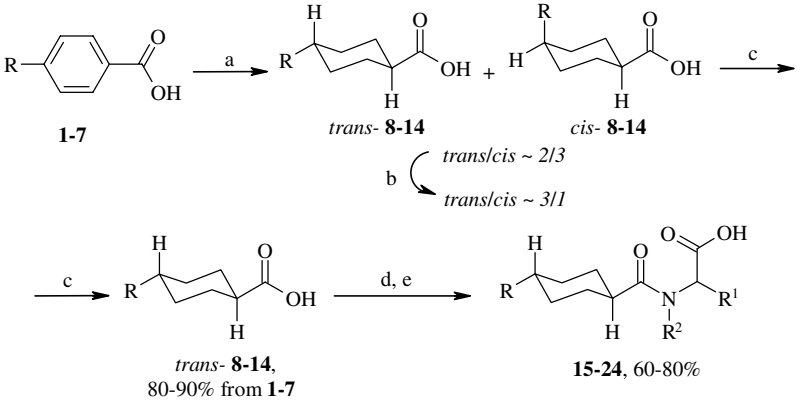
2. Results and discussion

Hydrogenation of arylcarboxylic acid derivatives using traditional heterogeneous catalysts based on platinum[7] or nickel,[8] is a well-documented process. For example, 4-*trans*-isopropylcyclohexanecarboxylic acid used for the synthesis of Nateglinide **1** has been obtained in 66% yield using PtO_2-catalyzed hydrogenation of 4-isopropylbenzoic acid followed by sodium hydride-mediated isomerization.[9] However, the reactions are carried out under severe conditions and are usually not selective, particularly in the case of alkylbenzoic acids with alkyl chains more than three carbon atoms in length. As a result, the yields of the desired products are often decreased. An alternative method of hydrogenation with the use of a sodium metal catalyst gives the desired product, albeit in low yields.[10]

It was reported that ruthenium-containing catalysts are more active in the hydrogenation of aromatic rings than platinum- or palladium-based catalytic systems.[11] Recently, we developed and applied in a pilot factory, an efficient carbon-supported ruthenium–nickel catalyst, RNC-5 (5% Ru–Ni/C, Ru:Ni=9:1).[12] In this work, we demonstrated the usefulness of this catalytic system for the convenient synthesis of several different stereomerically pure *trans*-4-alkylcyclohexanecarboxylic acids. 4-Alkylbenzoic acids **1**–**7** were hydrogenated in a 10% solution of NaOH in water in the presence of RNC-5 catalyst (Scheme 1). For all the acids **1**–**7** studied, mixtures of *trans*- and *cis*-isomers of the corresponding 4-alkylcyclohexanecarboxylic acids were formed in an approximate ratio of 2:3. Probably, the observed ratio of stereoisomers is due to the nonequilibrium state of the reaction mixture.[13] However, thermodynamic calculations indicate that the ratio of *trans*- and *cis*-isomers in an equilibrium state at a temperature of 513–573 K is equal to ~3:1.[13] In order to achieve the equilibrium state and increase the content of *trans*-isomer in the mixture, the catalyst was removed and the reaction mixture was kept at 260–280 °C and a pressure of 3.0–4.0 MPa for 2 h. The *trans*-isomer was isolated by crystallization from hexane. After isolation of the *trans*-isomer, the remaining mixture was subjected to repeated isomerization. After 3–4 cycles of isomerization–crystallization, up to 90% yields of individual *trans*-isomers of 4-alkylcyclohexanecarboxylic acids **8**–**14** were achieved (Scheme 1, Table 1).

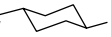
The ratio of *trans*- to *cis*-isomers in the hydrogenated mixtures were analyzed by ^{1}H NMR spectroscopy using the relative intensity of the signals due to the α-protons of the cyclohexane fragment. Thus the ^{1}H NMR spectrum of pure *trans*-4-methylcyclohexanecarboxylic acid **8** showed a triplet of triplets, centering around δ 2.00, corresponding to the α-proton. The ^{1}H NMR spectrum of the reaction mixture in the equilibrium state also contained signals from the same α-proton in the *cis*-isomer, which appeared as a triplet around δ 2.35 corresponding to averaged signals from the, a,e- and, e,a-conformers. When the methyl group was replaced with higher homologs, the degree of isomerization and ^{1}H NMR signals follows a pattern very similar to that shown by 4-methylcyclohexanecarboxylic acid. These characteristic ^{1}H NMR signals allowed us to analyse effectively the ratio of *trans*- to *cis*-isomers in the resulting products.

Upon treatment with thionyl chloride, acids **8**–**14** were quantitatively converted into the corresponding chlorides, which were used in the next step without purification. The target amino acid derivatives **15**–**24** were then obtained in 60–80% yields as pure (*S*)-stereoisomers using the Schotten–Baumann reaction between the acid



Scheme 1. Reagents and conditions: (a) H_2, 10% NaOH, H_2O, RNC-5, 140–150 °C, 3.0–4.0 MPa; (b) 10% NaOH, H_2O, 260–280 °C, 3.0–4.0 MPa; (c) crystallization, hexane, −10 °C; (d) $SOCl_2$, C_6H_6; (e) amino acid, 2 N NaOH, H_2O/1,4-dioxane.

Table 1. *trans*-4-Alkylcyclohexanecarboxylic acids synthesized in this work (Scheme 1)

Compound	R	Yield (%)
8	CH_3	90
9	C_3H_7	85
10	C_4H_9	82
11	C_5H_{11}	88
12	C_6H_{13}	85
13		80
14		80

chlorides and amino acids (Scheme 1, Table 2) as previously reported.[14] All the compounds synthesized were successfully identified and characterized using ^1H NMR, elemental, and mass-spectral analysis.[15]

In summary, we have described a convenient synthetic approach to the amino acid derivatives of *trans*-4-alkylcyclohexanecarboxylic acids, featuring a convenient RNC-5-catalyzed hydrogenation of 4-alkylbenzoic acids as the key step. Even in the case of bulky and long-chain 4-alkyl groups, the ruthenium–nickel-catalyzed hydrogenation followed by alkali-mediated isomerization provides high yields of pure *trans*-4-alkylcyclohexanecarboxylic acids as compared to alternative methods. Considering the ease of preparation of the initial reactants, convenient synthesis and isolation of products, and the overall good chemical yields of the described transformations, this route provides a new valuable entry to novel stereomerically pure peptidomimetics, which are of significant interest as promising physiologically active agents.

3. Experimental protocol for the hydrogenation of 4-alkylbenzoic acids

4-Alkylbenzoic acids **1**–**5** were purchased from Aldrich. 4-(*trans*-4-Alkylcyclohexyl)benzoic acids **6**, **7** were synthesized as reported.[16]

4-Alkylbenzoic acid (20 g), RNC-5 (3 g) and 10% aqueous NaOH (100 mL) were placed in an autoclave equipped with a high-speed mixer. The mixture was heated under an atmosphere of hydrogen at 140–150 °C and 3.0–4.0 MPa for 1 h. The catalyst was removed and the reaction mixture was heated at 260–280 °C and 3.0–4.0 MPa for an additional 2 h. The mixture was cooled to room temperature and acidified with conc. HCl until pH 2. The precipitate formed was filtered off and dried to afford a mixture, which contained ~75% of the *trans*-isomer. Pure *trans*-isomer was separated by recrystallization from hexane at −10 °C. The mother liquor was evaporated to dryness, and the residue was dissolved in 10% aqueous NaOH and subjected to isomerization. The repeated isomerization–crystallization cycles afforded *trans*-4-*n*-alkylcyclohexanecarboxylic acids **8**–**14** as white crystals in 80–90% yields.

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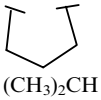
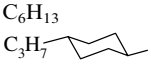
Table 2. Amino acid derivatives synthesized in this work (Scheme 1)

Compound	R	R^1	R^2	Yield from **8**–**14** (%)
15	CH_3	$(CH_3)_2CH$	H	80
16	CH_3	$(CH_3)_2CHCH_2$	H	60
17	CH_3			62
18	C_3H_7	$(CH_3)_2CH$	H	65
19	C_4H_9	$(CH_3)_2CH$	H	66
20	C_5H_{11}	$(CH_3)_2CH$	H	77
21	C_6H_{13}	$(CH_3)_2CH$	H	60
22	C_6H_{13}	$CH_3S(CH_2)_2$	H	68
23		$(CH_3)_2CH$	H	65
24		$(CH_3)_2CH$	H	68

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15. Satisfactory analytical data (^{1}H NMR, mass spectra) were obtained for all new compounds. For example: *trans*-4-methylcyclohexanecarboxylic acid (**8**): white crystals, mp 110–112 °C; ^{1}H NMR [DMSO-d_6+CCl_4 (1:3), 500 MHz]: δ = 10.00 (s, 1H), 2.02 (tt, 1H, J = 15.6, 3.8 Hz), 1.80 (m, 2H), 1.72 (m, 2H), 1.33 (dq, 2H, J = 12.0, 3.4 Hz), 1.30 (m, 1H), 0.92 (dq, 2H, J = 12.0, 4.3 Hz), 0.88 (d, 3, J = 7.2 Hz). Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.9; O, 22.5. Found: C, 67.5; H, 10.0; O, 22.5. 3-Methyl-(2*S*)-(*trans*-4-methylcyclohexylcarboxamido)butanoic acid (**15**): mp 184–186 °C; ^{1}H NMR [DMSO-d_6+CCl_4 (1:3), 500 MHz]: δ = 12.35 (s, 1H), 7.70 (d, 1H, J = 5.3 Hz), 4.15 (dd, 1H, J = 6.9, 5.3 Hz), 2.23 (m, 1H), 2.05 (m, 1H), 1.70 (m, 4H), 1.35 (m, 3H), 0.90 (m, 11H); EIMS: *m*/*z* 241 $[M]^+$, *m*/*z* (I_{rel}, %) = 196 (36), 142 (54), 125 (45), 97 (100), 72 (95), 55 (93) (93,5). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.7; H, 9.6; N, 5.8; O, 19.9. Found: C, 64.8; H, 9.7; N, 5.7; O, 19.8. 3-Methyl-2*S*-[*trans*-4-(*trans*-4-propylcyclohexyl)-cyclohexylcarboxamido]butanoic acid (**23**): mp 202–204 °C; ^{1}H NMR [DMSO-d_6, 500 MHz]: δ = 7.52 (s, 1H), 4.05 (m, 1H), 2.17 (t, 1H, J = 12.5 Hz), 2.03 (m, 1H), 1.70 (m, 8H), 1.30 (m, 4H), 1.12 (m, 3H), 0.95 (m, 6H), 0.83 (m, 11H); EIMS: *m*/*z* 351 $[M]^+$, *m*/*z* (I_{rel}, %) = 306 (30), 235 (42), 169 (100). Anal. Calcd for $C_{21}H_{37}NO_3$: C, 71.8; H, 10.5; N, 4.0; O, 13.7. Found C, 71.6; H, 10.6; N, 4.0; O, 13.8.
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